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Proposed Re-evaluation Decision PRVD2017-15

N-Octyl bicycloheptene dicarboximide (MGK-264) and its associated end-use products

Consultation Document

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Table of Contents

Overview 1
Proposed Re-evaluation Decision for N-Octyl bicycloheptene dicarboximide (MGK-264) 1
What Does Health Canada Consider When Making a Re-evaluation Decision? 2
What is MGK-264? 2
Health Considerations 2
Environmental Considerations 5
Value Considerations 6
Proposed Measures to Minimize Risk 6
International Regulatory Status of MGK-264 7
Next Steps 8
Science Evaluation 9
1.0 Introduction 9
2.0 Technical Grade Active Ingredient 9
2.1 Identity 9
2.2 Physical and Chemical Properties 10
2.3 Registered Uses 10
3.0 Impact on Human and Animal Health 10
3.1 Toxicology Summary 10
3.1.1 *Pest Control Products Act* Hazard Characterization 14
3.2 Dietary Exposure and Risk Assessment 15
3.2.1 Determination of Acute Reference Dose (ARfD) 16
3.2.2 Acute Dietary Exposure and Risk Assessment 16
3.2.3 Determination of Acceptable Daily Intake (ADI) 17
3.2.4 Chronic Dietary Exposure and Risk Assessment 18
3.3 Exposure from Drinking Water 18
3.3.1 Concentrations in Drinking Water 18
3.3.2 Drinking Water Exposure and Risk Assessment 18
3.4 Occupational and Non-Occupational Exposure and Risk Assessment 19
3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment 19
3.4.2 Non-Occupational Exposure and Risk Assessment 21
3.4.3 Occupational Exposure and Risk Assessment 23
3.5 Aggregate Exposure and Risk Assessment 26
3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment 26
3.5.2 Residential, Non-Occupational and Dietary Aggregate Exposure and Risk Assessment 27
3.6 Cumulative Assessment 28
4.0 Environmental Assessment 29
4.1 Fate and Behaviour in the Environment 29
4.2 Environmental Risk Characterization 29
4.2.1 Risks to Terrestrial Organisms 30
4.2.2 Risks to Aquatic Organisms 31
5.0 Value 31

6.0 Pest Control Product Policy Considerations 32
6.1 Toxic Substances Management Policy Considerations 32
6.2 Formulants and Contaminants of Health or Environmental Concern 32
7.0 Incident Reports 33
8.0 Proposed Re-evaluation Decision 33
8.1 Proposed Regulatory Action Related to Human Health 33
8.1.1 Proposed Mitigation Related to Toxicology 33
8.1.2 Proposed Mitigation Related to Dietary Exposure 33
8.1.3 Proposed Mitigation Related to Occupational and Residential Exposure 34
8.1.4 Residue Definition for Risk Assessment and Enforcement 35
8.2 Other Requirements 35
List of Abbreviations 37
Appendix I Toxicological Information for Health Risk Assessment 39
Table 1 Toxicology Profile for MGK-264 39
Table 2 Toxicology Reference Values for MGK-264 45
Appendix II Dietary Exposure and Risk Estimates for MGK-264 47
Table 1 Dietary Exposure and Risk Estimates for MGK-264 47
Appendix III Food Residue Chemistry Summary 49
Appendix IV Commercial Mixer/Loader/Applicator Risk Assessment 51
Table 1 Occupational Mixer/Loader/Applicator Exposure and Risk Assessment (Intermediate-Term) 51
Appendix V Non-Occupational Risk Assessment 53
Table 1 Residential Mixer/Loader/Applicator Exposure and Risk Assessment (Short-Term) 54
Table 2 Short-Term Postapplication Dermal Exposure from Hard and Soft Surfaces 55
Table 3 Short-Term Postapplication Dermal Exposure from Mattresses 58
Table 4 Short-Term Postapplication Dermal Exposure from Gardens and Trees[a] 58
Table 5 Short-Term Postapplication Dermal Exposure from Lawns and Turf[a] 59
Table 6 Short-Term Postapplication Dermal Exposure from Treated Pets Using Residential SOP Approach[a] 59
Table 7 Short-Term Postapplication Dermal Exposure from Treated Pets Using Chemical-Specific Data[a] 60
Table 8 Intermediate-Term Postapplication Dermal Exposure from Hard and Soft Surfaces61
Table 9 Long-term Postapplication Dermal Exposure from Hard and Soft Surfaces 62
Table 10 Long-Term Postapplication Dermal Exposure from Mattresses 62
Table 11 Short -Term Postapplication Inhalation Exposure from Aerosols 63
Table 12 Short -Term Postapplication Inhalation Exposure from Indoor Vapours 64
Table 13 Intermediate -Term Postapplication Inhalation Exposure for Metered Release Products 67
Table 14 Short-Term Postapplication Inhalation Exposure from Mosquito Abatement 68
Table 15 Long-Term Postapplication Inhalation Exposure from Indoor Surface Directed Sprays 69
Table 16 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments 69
Table 17 Short-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments 70

Table 18 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Lawns and Turf ... 71
Table 19 Short-Term Postapplication Object-to-Mouth Exposure to Children from Lawns and Turf ... 71
Table 20 Short-Term Postapplication Incidental Soil Ingestion Exposure for Children for Lawns and Turf ... 72
Table 21 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Treated Pets ... 72
Table 22 Intermediate-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments ... 72
Table 23 Intermediate-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments ... 73
Table 24 Long-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments ... 73
Table 25 Long-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments ... 74
Appendix VI Aggregate Risk Assessment ... 75
Table 1 Combined Short-Term Residential Applicator and Postapplication Exposure for Adults ... 75
Table 2 Short-Term Residential Aggregate Exposure and Risk Assessment ... 76
Table 3 Intermediate-Term Residential Aggregate Exposure and Risk Assessment ... 78
Table 4 Long-Term Residential Aggregate Exposure and Risk Assessment ... 79
Appendix VII Environmental Exposure and Risk Assessment ... 81
Table 1 Application Rates of MGK-264 Evaluated in the Risk Assessment ... 81
Table 2 Summary Fate and Behaviour of MGK-264 in the Environment ... 82
Table 3 Physical and Chemical Properties of MGK-264 ... 83
Table 4 Summary of Abiotic Transformation of MGK-264 ... 84
Table 5 Summary of Biotransformation Results for MGK-264 ... 84
Table 6 Summary of Acute and Chronic Toxicity Endpoints Reported for Non-Target Organisms ... 85
Table 7 Avian Acute Oral Toxicity of MGK-264 ... 86
Table 8 Avian Subacute Dietary Toxicity of MGK-264 ... 86
Table 9 Mammalian Acute Oral Toxicity of MGK-264 ... 86
Table 10 Mammalian Reproductive Toxicity of MGK-264 ... 86
Table 11 Freshwater Invertebrate Acute Toxicity of MGK-264 ... 86
Table 12 Freshwater Fish Acute Toxicity of MGK-264 ... 86
Table 13 Endpoints Used for Risk Assessment and the Species Uncertainty Factors Applied ... 87
Table 14 Screening Level Risk of MGK-264 to Birds ... 87
Table 15 Screening Level Risk of MGK-264 to Mammals ... 88
Table 16 Screening Level Surface Water EECs ... 88
Table 17 Screening Level Risk of MGK-264 to Aquatic Organisms ... 88

Table 18 Tier 1 Level Risk of MGK-264 to Aquatic Organisms from Mosquito Abatement Uses 89
Table 19 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria 89
Appendix VIII Label Amendments for End-Use Products Containing MGK-264 91
References 97

Overview

In Canada, pesticides are regulated under the *Pest Control Products Act*, administered by Health Canada's Pest Management Regulatory Agency (PMRA). All pesticides are registered (that is, approved) if a rigorous scientific assessment indicates that the health and environmental risks are acceptable and the products have value. The *Pest Control Products Act* also contains provisions for post-market reviews of registered pesticides, namely re-evaluation and special reviews, to assess whether pesticides continue to meet Health Canada's health and environmental standards, and whether they can continue to be used in Canada.

As part of the decision making process, before making a final decision, the PMRA consults with the members of the public and other interested stakeholders on all proposed major decisions such as new registrations, re-evaluations and special reviews. The PMRA encourages the public and stakeholders to participate in the consultation process. The proposed decisions are made based on the information available at the time, and the PMRA will consider the comments and information received during consultation using a science-based approach before making a final decision. The final decision will be published on the Pesticides and Pest Management portion of the Canada.ca website, and it will include a summary of the comments received during the consultation and the PMRA's responses to the comments.

The registration status of products and conditions of use of pesticide products on the market are not impacted by proposed re-evaluation or special review decisions. This may be the case only when final decisions are made. However, at any point during the re-evaluation or special review of a pesticide, the *Pest Control Products Act* allows the PMRA to cancel or amend the registration of registered pest control products, if there are reasonable grounds to believe this is necessary to deal with a situation that endangers human health or safety or the environment.

Proposed Re-evaluation Decision for N-Octyl bicycloheptene dicarboximide (MGK-264)

Using all currently available information and the most recent risk assessment methods, the PMRA has identified potential risks of concern for people (adults, youth and children) that may be exposed to MGK-264 while entering treated residential areas. As a result, the PMRA proposes measures to reduce potential risks to acceptable levels.

Any additional data/information submitted during the consultation period to further refine the health risk assessment will be considered, and may or may not result in a change to this proposal.

This Proposed Re-evaluation Decision is a consultation document[1] that summarizes the science evaluation for MGK-264 and presents the reasons for the proposed re-evaluation decision.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

This consultation document is presented in two parts. The Overview describes the regulatory process and key points of the evaluation, while the Science Evaluation provides detailed technical information on the assessment of MGK-264.

The PMRA will accept written comments on this proposal up to 90 days from the date of publication of this document. Please forward all comments to Publications (please see the contact information indicated on the cover page of this document).

What Does Health Canada Consider When Making a Re-evaluation Decision?

The PMRA's pesticide re-evaluation program considers potential risks, as well as value, of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2016-04, *Management of Pesticides Re-evaluation Policy*, presents the details of the current re-evaluation approach.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What is MGK-264?

MGK-264 is an insecticide synergist that is always co-formulated with one or more active ingredients belonging to synthetic pyrethroids and pyrethrins. It enhances the pesticide properties of other insecticides. MGK-264, co-formulated with other pyrethroids or pyrethrins, is registered to manage a wide spectrum of insect pests in stored food and feed, structures, companion animals, human habitat and recreational areas, human skin, clothing and proximal sites, and residential outdoors. Domestic-class products are applied using pressurized spray cans, roll-ons, pet shampoos and pump sprayers. Commercial-class products are applied using foggers, ultra-low volume equipment, pressurized sprayers and automated aerosol dispensers.

Health Considerations

Can Approved Uses of MGK-264 Affect Human Health?

Products containing MGK-264 are unlikely to affect your health when used according to the proposed label directions.

Potential exposure to MGK-264 may occur through the diet (food and drinking water), while handling and applying products containing MGK-264, or during contact with treated surfaces or animals. When assessing health risks, two key factors are considered: the levels at which no health effects occur and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). As such, sex and gender are taken into account in the risk assessment. Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Toxicology studies in laboratory animals describe potential health effects from varying levels of exposure to a chemical and identify the dose where no effects are observed. The health effects noted in animals occur at doses more than 100-times higher, and often much higher, than levels to which humans are normally exposed when pesticide products are used according to label directions.

In laboratory animals, MGK-264 was of low acute toxicity by the oral, dermal and inhalation routes. It was mildly irritating to the skin and to the eyes and did not cause an allergic reaction when applied to the skin.

For the re-evaluation, short- and long-term (lifetime) animal toxicity tests as well as information from the published scientific literature were assessed for the potential of MGK-264 to cause neurotoxicity, immunotoxicity, chronic toxicity, cancer, reproductive and developmental toxicity, and various other effects. The most sensitive endpoints used for risk assessment were effects on the liver, kidney, thyroid, and on bodyweight. Repeated inhalation exposure to MGK-264 affects the upper respiratory tract. There was no indication that young animals were more sensitive to health effects from MGK-264 than adult animals, or that MGK-264 damaged genetic material. However, extended dosing resulted in benign liver tumours in mice, and a slight increase in the incidence of thyroid tumours in rats. The risk assessment protects against the effects noted above and any other potential effects by ensuring that the levels of human exposure is well below the lowest level at which these occurred.

Pesticide Residues in Food and Drinking Water

Dietary risks from food and drinking water are not of concern when products containing MGK-264 are used according to the proposed label directions.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and water is acceptable if it is less than 100% of the acute reference dose (ARfD) or chronic reference dose (acceptable daily intake or ADI). An ADI is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects.

Dietary exposure to MGK-264 may occur from its use in areas where food can be handled (such as food handling establishments, restaurants), processed (such as processing facilities) or stored (such as storage warehouses). The use of MGK-264 on livestock intended for food production was not supported by the technical registrant; therefore, this use was not considered in the dietary assessment.

Dietary exposure to MGK-264 was estimated for the general population and different subpopulations using anticipated residues from simulated trials in food handling establishments and warehouses, and drinking water concentrations obtained from modelling. No acute and chronic risks of concern were identified.

The acute dietary exposure estimates (from food and drinking water) at the 95th percentile represent 4% of the ARfD for the general population and range from 2% (for adults aged 50+ years and females 13-49 years old) to 8% (for children 1-2 years old) of the ARfD for all population subgroups. The chronic dietary exposure estimate for the general population represents 13% of the ADI. Chronic exposure estimates for population subgroups range from 10% (for females aged 13-49 years and adults aged 50+ years) to 38% of the ADI (for children 1-2 years old). Thus, acute and chronic dietary risks are not of concern.

The PMRA proposes to add label statements to reduce potential residues in or on food, and to prohibit application to livestock intended for food production.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the specified MRL. Pesticide MRLs are specified for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in or on certain foods and serves as a food safety standard. The Canadian Food Inspection Agency is responsible for monitoring the Canadian food supply for pesticide residues and the determination of compliance with MRLs specified by Health Canada.

Residues of MGK-264 in all commodities are currently regulated under Subsection B.15.002(1) of the Food and Drugs Regulations, which requires that residues do not exceed 0.1 ppm (General MRL). No change to this regulatory status is being proposed.

Risks in Residential and Other Non-Occupational Environments

Risks are not of concern for people applying domestic products containing MGK-264 in or around homes or directly to animals.

People may be exposed to MGK-264 while applying domestic-class products in or around homes or directly to animals. No risks of concern to residential handlers were identified.

For some uses, risks are of concern when people are entering certain residential areas previously treated with products containing MGK-264. As a result, the PMRA proposes measures to reduce potential risks to acceptable levels, such as the cancellation of certain uses and domestic products.

People may be exposed to MGK-264 by dermal contact and inhalation, while performing activities in treated residential areas or contacting treated animals. This includes areas and animals treated by residential handlers using domestic-class products, as well as residential areas and animals treated by commercial applicators. Children may also be exposed to MGK-264 when playing on treated surfaces or with treated animals, and subsequently ingesting the product as a result of hand- or object-to-mouth transfer.

For children, risks of concern were identified from inhalation exposure when entering certain residential areas previously treated with products containing MGK-264. Risks of concern were also identified for adults, youth and children from inhalation exposure to the aerosols present immediately following indoor space spray applications. As a result, the PMRA proposes measures to reduce potential risks to acceptable levels. These measures are listed in the Proposed Measures to Minimize Risk section of the Overview.

Aggregate risks are not of concern when the above-noted proposed mitigation measures are considered.

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). No aggregate risks of concern were identified for MGK-264 when the above-noted proposed mitigation measures are considered.

Occupational Risks to Handlers and Postapplication Workers

Risks are not of concern when workers mix, load and apply products containing MGK-264 according to the proposed label directions.

Risks to workers associated with mixing, loading and applying activities are not of concern when mitigation measures (personal protective equipment, including chemical-resistant gloves and a respirator) are considered. No measured exposure data were available for application with handheld foggers/mistblowers, or handheld ultra-low-volume aerosol generators/mechanical aerosol generators (space sprays). As such, it is proposed to prohibit this application equipment on related product labels.

Risks are not of concern for workers entering sites or handling animals that were previously treated with products containing MGK-264 according to the proposed label directions.

Occupational postapplication risk assessments for MGK-264 consider exposure to workers entering treated sites (for example, food processing plants, warehouses, office buildings) or handling treated animals. No risks of concern were identified provided that workers do not enter the treated site until two hours after space spray applications.

Environmental Considerations

What Happens When MGK-264 Is Introduced into the Environment?

When used according to label directions, products containing MGK-264 are not expected to pose risks of concern to the environment.

MGK-264 enters the environment in the form of spray droplets, but breaks down rapidly once in the air. It is, therefore, unlikely that MGK-264 will persist long enough to reach soil or water. The chemical properties of MGK-264 indicate that it may accumulate in animal tissues, but this

is not expected since MGK-264 is applied as an ultra-low volume spray mist, which involves putting very small amounts of liquid into the air as a fine mist of droplets. When applied in this manner, MGK-264 will not persist in the air long enough to deposit onto soil or water, and will not be available for bioaccumulation.

No risks of concern to organisms or the environment were identified during the risk assessment.

Value Considerations

What is the Value of MGK-264?

MGK-264 is a synergist that is used to increase the effectiveness of other active ingredients belonging to the pyrethroid and pyrethrins group. The use of synergists when co-formulated with other active ingredients improves the potency of the other insecticides, thus reducing the amount of these insecticides required to manage the insect pests.

Proposed Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human health and the environment. These directions must be followed by law. As a result of the re-evaluation of MGK-264, the PMRA proposes further risk-reduction measures.

Human Health

To protect homeowners and those entering treated residential and commercial areas, the following measures are proposed:

For domestic-class products:

- Cancellation of dust products
- Cancellation of aerosol products for use as a metered release space spray
- Cancellation of space spray uses for aerosol products
- Maximum guarantee limited to 0.4% MGK-264 for aerosol products registered for indoor treatment of fleas, ticks, and carpet beetles
- Label directions to include definition of broadcast and spot/band treatment, unless similar information or more restrictive application instructions are already present

For commercial-class products:

- Maximum space spray application rate limited to 0.055 g a.i./m^3 for liquid formulations in certain residential areas (dwellings such as houses, apartments, or in guest rooms of hotels and motels)
- Maximum guarantee limited to 3.3% MGK-264 for aerosol products for use as a metered release space spray
- Prohibit aerosol products for use as a metered release space spray in areas where children may be present for more than four hours per day

- Entry into treated sites in both residential and commercial areas following an indoor space spray application must not occur until two hours after application. The commercial applicator is responsible for notifying workers, the homeowner, and others of this requirement.
- Label directions to include definition of broadcast and spot/band treatment, unless similar information or more restrictive application instructions are already present

To protect mixer/loader/applicators, the following measures are proposed:

- Prohibit the use of handheld ultra-low-volume aerosol generators/mechanical aerosol generators for space sprays
- Prohibit the use of handheld foggers/mistblowers
- Additional protective equipment when mixing, loading or applying by handheld equipment or truck-mounted sprayers

To protect bystanders from spray drift, the following measures are proposed:

- Statement to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift in non-target areas.

To protect consumers from potential residues in or on food, the following measures are proposed:

- All commercial-class labels to include the statement: "Application on livestock intended for food production is prohibited."
- All labels to include the statement: "Cover or remove exposed food and food handling surfaces prior to application."

To protect human health, the PMRA proposes to limit the maximum guarantee for certain products. In order to retain products that need to be reformulated, registrants would be required to provide a scientific rationale and/or efficacy data to demonstrate that the insecticidal efficacy of their products is not impacted at the reduced MGK-264 guarantee.

Environment

- No risk mitigation measures are proposed.

International Regulatory Status of MGK-264

The PMRA routinely works collaboratively with other member countries in the Organisation for Economic Co-operation and Development (OECD) on the regulation of pesticides. As part of the re-evaluation of an active ingredient, the PMRA takes into consideration recent developments and new information on the status of a pesticide in other jurisdictions. MGK-264 is currently acceptable for use in other OECD member countries, including Australia and the United States. No decision by an OECD member country to prohibit all uses of MGK-264 for health or environmental reasons has been identified at this time.

Next Steps

During the consultation period, registrants and stakeholder organizations may submit further data that could be used to refine risk assessments (exposure or use information), which could result in revised risk-reduction measures. Stakeholders who are planning to provide information of this type are advised to contact the PMRA early in the consultation period, for advice on studies or information that could be submitted to help refine the relevant risk assessments.

Before making a final re-evaluation decision on MGK-264, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will then publish a Re-evaluation Decision[2] that will include the decision, the reasons for it, a summary of comments received on the proposed decision and the PMRA's response to these comments.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Science Evaluation

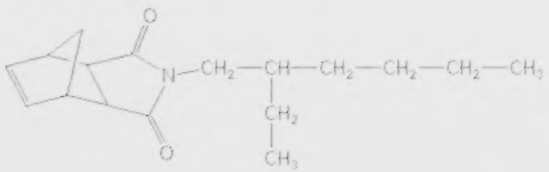
1.0 Introduction

MGK-264 is an insecticide synergist that is always co-formulated with one or more active ingredients belonging to synthetic pyrethroids and pyrethrins. It does not belong to any Insecticide Resistance Management mode of action group. The mode of action of MGK-264 is not fully understood, but it is suggested that it acts by binding directly to the enzymes in the insect pests which break down pyrethrins and synthetic pyrethroids. By inhibiting this breakdown, MGK-264 contributes to the effectiveness of other insecticides.

Following the re-evaluation announcement for MGK-264, the technical registrant and primary data provider in Canada indicated continued support for all uses included on the labels of end-use products, with the exception of animals for food production.

2.0 Technical Grade Active Ingredient

2.1 Identity

Common name	*N*-octyl bicycloheptene dicarboximide
Function	Insecticide
Chemical Family	Insecticide synergist
Chemical name	
1 **International Union of Pure and Applied Chemistry (IUPAC)**	*N*-(2-ethylhexyl)-8,9,10-trinorborn-5-ene-2,3-dicarboximide
2 **Chemical Abstracts Service (CAS)**	2-(2-ethylhexyl)-3a,4,7,7a-tetrahydro-4,7-methano-1*H*-isoindole-1,3(2*H*)-dione
CAS Registry Number	113-48-4
Molecular Formula	$C_{17}H_{25}NO_2$
Structural Formula	
Molecular Weight	275.4
Purity of the Technical Grade Active Ingredient	95.72%
Registration Number	18524

2.2 Physical and Chemical Properties

Property	Result
Vapour pressure at 25°C	2.4 mPa
Ultraviolet (UV) / visible spectrum	λ_{max} (in methanol) = 295 nm
Solubility in water at 20-25°C	Practically insoluble
n-Octanol/water partition coefficient	Log K_{ow} = 3.61 (*cis*- isomer); 3.80 (*trans*-isomer)
Dissociation constant	Does not contain any dissociable moiety.

2.3 Registered Uses

As of 10 February 2017, one technical grade active ingredient product, seven manufacturing products, 37 commercial-class products and 162 domestic-class products containing MGK-264 were registered in Canada. Formulations include dust, emulsifiable concentrates, liquids, pressurized products and solutions. MGK-264 labels can be accessed through the PMRA's label transcription service.[3] All uses supported by the registrants at the time of re-evaluation initiation were considered in the risk assessments of MGK-264.[4]

3.0 Impact on Human and Animal Health

3.1 Toxicology Summary

A detailed review of the toxicological database for MGK-264 was conducted. The database is extensive, providing sufficient information for hazard assessment purposes. Although several studies were dated, the majority of the studies were carried out in accordance with currently accepted international testing protocols and Good Laboratory Practices. Overall, the scientific

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[3] PMRA's label transcription service is available online through the product label search on the Pesticides and Pest Management portion of Health Canada's website: http://pr-rp.hc-sc.gc.ca/ls-re/index-eng.php. Pesticide labels can also be accessed on a mobile device using the pesticide label app: https://www.canada.ca/en/health-canada/services/consumer-product-safety/pesticides-pest-management/registrants-applicants/tools/pesticide-label-search.html.

[4] Maximum application rates from Canadian labels or the United States MGK-264 Master Label were used in the risk assessments. If application rates from the MGK-264 Master Label were mitigated in the United States Environmental Protection Agency (USEPA) Reregistration Eligibility Decision document for MGK-264, then these reduced rates were selected for the risk assessments. Furthermore, if the PMRA identified risks of concern at maximum application rates from the MGK-264 Master Label, the Canadian rates, if lower, were then selected for the risk assessments. When application rates were not available from Canadian or American labels, the PMRA calculated application rates based on product and use information. The USEPA has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures. These assumptions were used in the absence of, or as a supplement to, chemical- and/or site-specific data, as outlined in the Standard Operating Procedures (SOP) for Residential Pesticide Exposure Assessments.

quality of the data is high and the database is considered adequate to define the majority of toxic effects that may result from exposure to MGK-264.

MGK-264 radiolabelled in either the norbornene-2, 3-^{14}C or hexyl-1-^{14}C positions was rapidly absorbed, distributed and excreted as metabolites in the urine and feces of orally exposed rats. When rats were given a single low or high gavage dose, or multiple gavage doses of MGK-264 radiolabeled in either position, blood levels of radioactivity peaked at 4-6 and 6 hours for males and females, respectively.

Seven days following a dose of radiolabelled MGK-264, tissue retention was minimal in all dosing regimens, with the highest radioactivity levels occurring in the intestines, carcass and liver.

MGK-264 was extensively metabolized prior to elimination. Unchanged MGK-264 was not detected in the urine, and only small amounts were present in the feces. Major metabolites included carboxylic acids produced by either β- or ω-1 oxidation of the side chain, and stable epoxides, which were formed by oxidation of the norbornene double bonds.

The half-life of blood radioactivity was approximately 4 hours with norbornene -2, 3-^{14}C, and approximately 7 hours with hexyl-1-^{14}C, respectively, in rats; no sex difference was noted. Elimination via expired air was negligible. With single or repeat administration of low doses of MGK-264 radiolabeled in either position, male rats eliminated comparable amounts of the dose in urine and feces. Female rats excreted a larger proportion of the dose in urine than males. Greater urinary elimination was observed in both sexes following the administration of a single high dose. The majority of the administered radioactivity was recovered within the first 36 hours in urine and 48 hours in feces.

In acute toxicity studies, MGK-264 was of low toxicity by the oral and inhalation routes of exposure in rats, and of low dermal toxicity in rabbits. MGK-264 was a mild skin and eye irritant in rabbits. MGK-264 did not induce a dermal sensitization response in a Modified Buehler test in guinea pigs.

In short-term dietary toxicity studies in mice, rats and dogs, the liver was consistently affected and usually accompanied by decreases in food consumption, bodyweight gain or bodyweight. The liver findings in mice progressed from increased organ weight at lower doses, to discolored liver, biliary stasis, and hepatocellular hypertrophy at higher doses. Histopathology was not performed in the rat studies, but liver weights were affected in a dose related manner. Among the species tested, dogs were the most sensitive. A supplementary 61-day dietary study in dogs revealed a variety of changes in organ weights and clinical chemistry parameters. At the high dose, increased liver enzymes were accompanied by the observation of dark liver and bile concretions in the gallbladder; no histopathology was performed in this study. In a 1-year dietary dog study, liver toxicity was apparent in the form of increased liver weight, hepatocellular hypertrophy, biliary stasis, elevated liver enzymes and mononuclear cell foci in parenchyma.

There was no systemic toxicity in a rat 21-day dermal study conducted at the limit dose of testing, or in a rabbit 90-day dermal toxicity study that used lower doses than those in the rat study. A marginal liver weight increase noted in high-dose rats indicated that longer exposures may lead to adverse effects. Dermal effects consisting of irritation, hyperplasia of the epidermis and follicular epithelium in rats, and erythema and edema in rabbits, were localized to the treatment site, with a dose dependent increase in severity.

In a 90-day rat inhalation toxicity study, metaplasia/hyperplasia and keratinization of the larynx mucosal epithelium occurred in all MGK-264 treated animals. Inactivity, excessive salivation, nasal discharge, and red facial staining were seen only in the high-dose group. In the nasoturbinate and nasopharynx epithelium, goblet cells responded with hypertrophy/hyperplasia accompanied by increased secretion of intracytoplasmic eosinophilic material. The incidence and severity of all these findings occurred in a dose-responsive manner. Following a 90-day recovery period in high-dose animals only, there was incomplete recovery of the stratified squamous epithelium of the larynx mucosa.

In a long-term dietary toxicity study in mice, treatment with MGK-264 resulted in bodyweight reduction and changes in the liver. Survival was also reduced in high-dose animals. Liver effects in the mid-dose males and high-dose females consisted of increased liver weights, biliary stasis, calculi in the gallbladder and an increased incidence of nodules/masses. In addition, hepatocellular hypertrophy in high-dose males and females, and portal duct proliferation, portal mononuclear cell infiltration, spongiosis and vacuolar changes in high-dose males, were noted.

The incidence of benign liver tumors (hepatocellular adenoma) was statistically significantly increased in high-dose males, but not females. There was a statistically significant positive trend for adenoma in both sexes. The incidence for males, but not females, was higher than historical control incidence. There was no dose-related increase in the incidence of hepatocellular carcinomas in either male or female mice; the incidence of this tumour was within historical control values. Although there was a statistically significant increase in combined adenoma/carcinoma in mid-dose males, and in high-dose males and females, this increase was due to the increase in adenomas only.

In a 24-month dietary chronic/oncogenicity study in rats, the high-dose animals had consistently lower bodyweights than their respective controls throughout the study. There was a statistically significant trend for lower survival among male groups. Liver was the target organ with dose-related findings that included increased incidences of liver foci together with hepatocellular hypertrophy, bile stasis, and bile duct cysts. An increased incidence of brown pigment in the convoluted tubule epithelium of the kidney was also noted in females of mid- and high-dose groups. Additionally, in high-dose females, red blood cell parameters were depressed, and serum blood urea nitrogen, cholesterol, total protein and globulin were increased. There was a statistically significant increased incidence (pairwise and trend) of thyroid follicular cell adenomas in mid- and high-dose males and in combined adenomas/carcinomas for high-dose males. The incidence of these thyroid tumors was just outside the historical control range. There was no treatment-related increase in the incidence of thyroid follicular cell carcinomas.

There was no evidence of genotoxicity in a battery of in vivo and in vitro assays conducted with MGK-264.

A threshold approach to cancer risk assessment for the tumours in rats and mice was considered appropriate based on several factors, which included adequate dosing for the assessment of carcinogenicity in both species. All tumours of interest were considered benign in nature, with no indication of a progression to malignant neoplasms in either species. The incidences were similar to or just beyond historical control ranges, and genotoxicity studies were negative.

In guideline gavage rat and rabbit developmental toxicity studies, maternal toxicity consisted of decreased bodyweight and food consumption. At higher doses in the range finding studies, deaths, abortions (rabbits) and resorptions (rats) were noted. Rabbit dams were more sensitive than rats to these effects. Overall, there was no evidence of adverse effects on the developing fetus or sensitivity of the young in the available developmental toxicity studies.

Reproductive toxicity was investigated in two dietary 2-generation studies in rats. In the older study, a sustained decrease in bodyweight/bodyweight gain was seen in the high-dose parents (P and F1), and to some extent, in the mid- and low-dose parents (F1). A treatment-related increase in parental mortality and extensive liver lesions (calculus, hyaline droplet, brown pigment, portal bile duct proliferation) were also observed in the high-dose group. In addition, an increased incidence of hepatocyte hypertrophy occurred in both sexes of the mid- and high-dose groups (P and F1) and in low-dose females (F1 only). Dams in the high-dose group had a lower gestation index and longer copulatory interval at the second mating.

In offspring, pup bodyweight was decreased at postnatal (PND) day 21 in the low-dose and at PND 7 or 14 in the mid-and high-dose groups respectively. This effect was considered treatment-related in all groups although the dose response was not clear. However, there is a low level of concern for this effect because it was not replicated in a second 2-generation reproductive toxicity study.

A more recent dietary 2-generation reproductive toxicity study in rats (2009) confirmed liver as a target organ of toxicity. In parental animals, liver effects progressed from adaptive changes at the low-dose to liver enlargement, distinct lobulation, increased incidence/severity of periportal/centrilobular hypertrophy, and fat storage at higher dose levels in both generations. Other treatment-related effects in the mid- and high-dose groups included effects on the kidney (increased weight, brownish pigment, and hyaline droplets), thyroid gland (follicular cell hypertrophy and/or colloidal alterations (P and F1)) and a decrease in bodyweight.

In offspring in this study, decreases in body and organ weights from PND 14 onward were observed in high-dose male pups. In high-dose female pups, vaginal opening was delayed by 4 days. No evidence of increased sensitivity of the young was indicated. However, the low viability and lactation indices in the control group and across generations among treated groups may have affected the interpretation of the offspring data.

With respect to reproductive parameters, a slight decrease in the number of implantations and litter size in the high-dose group may be related to altered luteinisation of the ovaries/corpora lutea.

Considering both studies, it was concluded that there is no evidence of increased sensitivity of the young.

No evidence of selective neurotoxicity was noted in the toxicology database.

Results of the toxicology studies conducted on laboratory animals with MGK-264 are summarized in Table 1 of Appendix I. The toxicology reference values for use in the human health risk assessment are summarized in Table 2 of Appendix I.

Cancer Assessment

An increased incidence of liver adenomas in male mice, and of thyroid follicular adenomas in male rats, was observed following chronic dosing. The relatively low incidence of these tumors, a lack of progression to carcinoma, and negative genotoxicity assays, support a threshold risk assessment approach for these tumors.

The selected toxicology reference value and target margin of exposure (MOE) provides a margin of 5700 to the no observed adverse effect level (NOAEL) for hepatocellular adenomas observed in male mice, and a margin of 2100 to the NOAEL for thyroid follicular cell adenomas observed in male rats.

3.1.1 *Pest Control Products Act* Hazard Characterization

For assessing risks from potential residues in food or from products used in or around homes or schools, the *Pest Control Products Act* requires the application of an additional 10-fold factor to threshold effects to take into account completeness of the data with respect to the exposure of, and toxicity to, infants and children, and potential prenatal and postnatal toxicity. A different factor may be determined to be appropriate on the basis of reliable scientific data.

With respect to the completeness of the toxicity database as it pertains to the toxicity to infants and children, the standard complement of studies, including, developmental toxicity studies in rats and rabbits and two reproductive toxicity studies in rats, were available. With respect to potential prenatal and postnatal toxicity, there was no evidence of increased sensitivity of fetuses or offspring compared to parental animals in these studies.

In the guideline rat and rabbit developmental toxicity studies, maternal toxicity consisted of decreased bodyweight and food consumption. In rabbits, these findings were observed in the dose range-finding study at a higher dose than the highest dose used in the definitive rabbit study; no effects on dams were observed in the latter study. The rabbit dose range-finding study also demonstrated maternal mortality and abortions at these higher doses. In the guideline rat and rabbit developmental studies, no developmental effects on the fetus were noted.

In an older (1990) reproductive toxicity study, body weight effects on offspring were noted at all dose levels. However, no clear dose-response was apparent and these findings occurred in the presence of maternal toxicity, predominantly in the form of liver changes that progressed from adaptive at the low dose, to clearly adverse in mid- and high-dose groups. These same parental effects occurred in a second reproductive toxicity study (2009); however, offspring bodyweights were not affected up to the high dose. Although low viability and lactation indices in control and treated groups for both generations compromised data interpretation, based on the available data, it was concluded that there was no evidence that the young animal was more sensitive than the adult animal.

Overall, endpoints in the young were well-characterized and not considered serious in nature. With respect to potential prenatal and postnatal toxicity, no evidence of increased sensitivity of fetuses or offspring was noted compared to parental animals in these studies. On the basis of this information, the *Pest Control Products Act* factor was reduced to 1-fold.

3.2 Dietary Exposure and Risk Assessment

In a dietary exposure assessment, the PMRA determines how much of a pesticide residue, including residues in milk and meat, may be ingested with the daily diet. Exposure to MGK-264 from potentially treated imported foods is also included in the assessment. Dietary exposure assessments are age specific and incorporate the different eating habits of the population at various stages of life (infants, children, adolescents, adults and seniors). For example, the assessments take into account differences in children's eating patterns, such as food preferences and the greater consumption of food relative to their body weight when compared to adults. Dietary risk is then determined by the combination of the exposure and the toxicity assessments. High toxicity may not indicate high risk if the exposure is low. Similarly, there may be risk from a pesticide with low toxicity if the exposure is high.

The PMRA considers limiting use of a pesticide when exposure exceeds 100% of the reference dose. The PMRA's Science Policy Note SPN2003-03, *Assessing Exposure from Pesticides, A User's Guide*, presents detailed acute, chronic and cancer risk assessment procedures.

Sufficient information was available to adequately assess the dietary risk from exposure to MGK-264. Acute and chronic dietary exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database™ (DEEM-FCID™, Version 4.02, 05-10-c) program which incorporates consumption data from the National Health and Nutrition Examination Survey, What We Eat in America 2005-2010 available through the Centers for Disease Control and Prevention's National Center for Health Statistics. Further details on the consumption data are available in Science Policy Note SPN2014-01, *General Exposure Factor Inputs for Dietary, Occupational and Residential Exposure Assessments*. For more information on dietary risk estimates and the residue chemistry information used in the dietary assessment, see Appendices II and III.

3.2.1 Determination of Acute Reference Dose (ARfD)

General Population (including pregnant women, infants and children)

To estimate acute dietary risk, the developmental toxicity study in rabbits with a maternal NOAEL of 100 mg/kg bw/day, the highest dose tested in a guideline study, was selected. At 300 mg/kg bw/day, the lowest dose tested in the range finding study, slight maternal bodyweight loss was observed. These effects occurred following the first few days of dosing and are, therefore, relevant to an acute risk assessment. Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. Thus, the composite assessment factor (CAF) is 100.

The ARfD is calculated according to the following formula:

$$\text{ARfD} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{100 \text{ mg/kg bw}}{100} = 1 \text{ mg/kg bw of MGK-264}$$

3.2.2 Acute Dietary Exposure and Risk Assessment

The acute dietary risk was calculated considering the highest ingestion of MGK-264 that would be likely on any one day, and using food and drinking water consumption and food and drinking water residue values. The expected intake of residues is compared to the ARfD, which is the dose at which an individual could be exposed on any given day and expect no adverse health effects. When the expected intake of residues is less than the ARfD, the acute dietary exposure is not of concern.

The acute dietary exposure and risk assessments were conducted for the general population and all subpopulations. Residue values used in this assessment were taken from simulated warehouse trials (anticipated residues on food in the warehouse scenario) as they represent the scenario where the highest MGK-264 residue levels were found. Trials in simulated food handling establishments generally showed lower residue levels (<0.1 ppm, which is the limit of quantitation) than the warehouse scenario. The use directions in food handling establishments require that all food items be removed or covered prior to product application. In contrast, the use directions specified in the warehouse study allows product application to uncovered bags containing the following foods: peanuts, nuts, beans (including cocoa), seeds, and copra. In addition, detectable MGK-264 residue levels are assumed to occur in cereal grains and dried fruits as fogging products containing MGK-264 may be used in areas containing uncovered bags of cereal grains and in rooms where dried fruits are stored or processed. The available residue data were translated to other commodities using an approach to ensure that residue estimates would not be underestimated. In general, the highest residue level from the warehouse trial was translated to all foods that may be treated in warehouse storage. The exception to this was made for legume vegetables, cocoa beans, coffee beans and sugar, where the submitted simulated trial results for navy beans and granulated sugar were used. All other food items were assumed to have limit of quantitation (LOQ) residue levels (0.1 ppm) resulting from the uses in food handling establishments.

Available U.S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data showed that residues in monitored samples were mostly not detected. For the few commodities with detected MGK-264 residues, the monitoring residue values were mostly lower than the trial residues used in the assessment; otherwise the monitoring residue was used in the exposure assessment. The acute analysis was conducted using maximum (highest) trial or monitoring residue levels. All food commodities were assumed to be treated (100% treated; no refinement for percent crop treated). Drinking water contribution to the exposure was accounted for by direct incorporation of the appropriate estimated environmental concentration (EEC), obtained from water modelling (see Section 3.3), into the dietary exposure evaluation model (DEEM). DEEM default processing factors were applied.

The acute dietary (food and drinking water) exposure estimates, at the 95th percentile, are approximately 4% of the ARfD for the general population and in the range from 2% (for females 13-49 years old and adults aged 50+ years) to 8% of the ARfD (for children 1 to 2 years old), and are therefore not of concern.

3.2.3 Determination of Acceptable Daily Intake (ADI)

General Population (including pregnant women, infants and children)

To estimate risk from repeated dietary exposure, the NOAEL of 7.4 mg/kg bw/day from the 1-year dietary study in dogs was selected. At the lowest observed adverse effect level (LOAEL) of 33 mg/kg bw/day, effects on the liver were noted (increased weight, hepatocellular hypertrophy, biliary stasis, elevated liver enzyme levels, mononuclear cell foci in parenchyma). Standard uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability were applied. As discussed in the *Pest Control Products Act* Hazard Characterization section, the *Pest Control Products Act* factor was reduced to 1-fold. Thus, the composite assessment factor (CAF) is 100.

The ADI is calculated according to the following formula:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{CAF}} = \frac{7.4 \text{ mg/kg bw/day}}{100} = 0.07 \text{ mg/kg bw/day of MGK-264}$$

The ADI provides a margin of 5700 to the NOAEL for hepatocellular adenomas observed in male mice, and a margin of 2100 to the NOAEL for thyroid follicular cell adenomas observed in male the rats.

3.2.4 Chronic Dietary Exposure and Risk Assessment

The chronic dietary risk was calculated using the average consumption of different foods and drinking water and the average residue values on those foods and in drinking water. This estimated exposure was then compared to the ADI. The ADI is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is believed to have no significant harmful effects. When the estimated exposure is less than the ADI, the chronic dietary exposure is not of concern.

The chronic assessment was conducted for the general population and all subpopulations using average residues from simulated trials in warehouses and food handling establishments or from PDP monitoring, DEEM default processing factors and assuming that all commodities were 100% treated. Drinking water contribution to the exposure was accounted for by direct incorporation of the appropriate EEC, obtained from water modelling (see Section 3.3), into DEEM.

The chronic dietary (food and drinking water) exposure estimate for the general population represents approximately 13% of the ADI. Exposure estimates for population subgroups range approximatively from 10% (for females aged 13-49 years and adults aged 50+ years) to 38% of the ADI (for children 1-2 years old). Thus, chronic exposure to MGK-264 residues in food and drinking water is not of concern.

3.3 Exposure from Drinking Water

Residues of MGK-264 in potential drinking water sources were estimated from modelling.

3.3.1 Concentrations in Drinking Water

MGK-264 is not registered for use on agricultural crops, but it is approved for general outdoor and mosquito abatement uses. Therefore, modelling of estimated environmental concentrations (EECs) of MGK-264 residues in potential drinking water sources was required. EECs in surface water were calculated using the Pesticide in Water Calculator model on a standard Level 1 scenario, a small reservoir. EECs in groundwater were calculated using the Pesticide in Water Calculator model across Canada. All scenarios were run for 50 years. The modelling covers only general outdoor and mosquito abatement uses. The EECs resulting from this Level 1 assessment were calculated using conservative inputs with respect to application rate and timing, and geographic scenario. The highest groundwater daily peak EEC value of 0.051 ppm and yearly average EEC value of 0.051 ppm for MGK-264 (please refer to the Environmental Assessment Section of this document for details) were used in the acute and the chronic dietary exposure assessments, respectively.

3.3.2 Drinking Water Exposure and Risk Assessment

Drinking water exposure estimates were combined with food exposure estimates, with EEC point estimates incorporated directly in the dietary (food + drinking water) assessments. Please refer to sections 3.2.2 and 3.2.4 for details.

3.4 Occupational and Non-Occupational Exposure and Risk Assessment

Occupational and non-occupational risk is estimated by comparing potential exposures with the most relevant endpoint from toxicology studies to calculate a MOE. This is compared to a target MOE incorporating uncertainty factors protective of the most sensitive subpopulation. If the calculated MOE is less than the target MOE, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required.

If a common toxic effect (for example, specific liver toxicity) occurs with multiple routes of exposure, risks from these routes are aggregated using an aggregate risk index (ARI). The ARI is a method of measuring combined risk when exposure occurs via multiple routes or pathways and different toxicological points of departure and uncertainty factors are defined for each route. The ARI is an extension of the MOE concept. As with the MOE, risk increases as the ARI decreases. ARIs greater than or equal to one do not require mitigation. If the calculated ARI is less than one, it does not necessarily mean that exposure will result in adverse effects, but mitigation measures to reduce risk would be required. Further information on conducting aggregate exposure and risk assessments can be found in Science Policy Note SPN2003-04, *General Principles for Performing Aggregate Exposure and Risk Assessments*.

3.4.1 Toxicology Endpoint Selection for Occupational and Non-Occupational Risk Assessment

Dermal Exposure:

For **short-term dermal risk assessment,** the rat 21-day dermal toxicity with a NOAEL of 1000 mg/kg bw/day (limit dose) was selected. At this dose level, there was a marginal increased liver weight in the absence of histopathology or clinical chemistry changes.

For **intermediate-term dermal risk assessment,** the rabbit 90-day dermal study with a NOAEL of 100 mg/kg bw/day, was selected. No systemic toxicity was observed. Higher doses were excessively irritating to the skin.

For **long-term dermal risk assessment,** the one-year dog study with a NOAEL of 7.4 mg/kg bw/day was selected.

For all dermal scenarios (occupational and residential), a target MOE of 100 to account for inter-species extrapolation and intra-species variability was considered appropriate. For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as outlined in the *Pest Control Products Act* Hazard Characterization section.

Inhalation Exposure:

The most appropriate study for **short-, intermediate-, and long-term inhalation risk assessment** is the 90-day inhalation toxicity study in rats, in which a lowest observable adverse effect concentration (LOAEC) of 0.01 mg/L (1.9 mg/kg bw/day) was based on hyperplasia/metaplasia and keratinization of the larynx epithelium observed at all dose levels tested.

For short- and intermediate-term exposure scenarios, the target MOE is 300, which includes uncertainty factors of 10-fold for inter-species extrapolation, 10-fold for intra-species variability, and a 3-fold uncertainty factor for lack of a no observable adverse effect concentration (NOAEC).

For long-term exposure scenarios, the target MOE is 1000, which, in addition to the factors outlined above, includes a 3-fold uncertainty factor for extrapolation from intermediate- to long-term exposure based on the lack of full recovery from toxicological effects after a 90-day recovery period in the 90-day inhalation toxicity study.

For residential scenarios, the *Pest Control Products Act* factor was reduced to 1-fold as outlined in the *Pest Control Products Act* Hazard Characterization section.

Non-Dietary Oral Ingestion (Children, Short-Term):

For assessment of short- and intermediate-term incidental (non-dietary) oral exposure, the rat 2-generation reproductive toxicity study was selected for risk assessment, in which a NOAEL of 33 mg/kg bw/day for parental animals was identified based on liver, kidney and thyroid effects at 137 mg/kg bw/day. The target MOE is 100 and includes uncertainty factors of 10-fold for inter-species extrapolation, and 10-fold for intra-species variability. The *Pest Control Products Act* factor was reduced to 1-fold for residential scenarios, as discussed in the *Pest Control Products Act* Hazard Characterization section.

For assessment of long-term incidental (non-dietary) oral exposure, the 1-year dog study was selected, which established a NOAEL of 7.4 mg/kg bw/day based on liver toxicity (increased liver weight, hepatocellular hypertrophy, biliary stasis and elevated enzymes) at the LOAEL of 33 mg/kg bw/day. The target MOE is 100, which includes uncertainty factors of 10-fold for inter-species extrapolation and 10-fold for intra-species variability. The *Pest Control Products Act* factor was reduced to 1-fold for residential scenarios, as discussed in the *Pest Control Products Act* Hazard Characterization section.

Dermal Absorption:

For short and intermediate-term durations of exposure, a dermal absorption value was not required as the toxicological point of departure used for the dermal risk assessment is based on a dermal study.

For long-term durations of exposure, a dermal absorption value of 10% was used for MGK-264 based on two human in vivo studies submitted to the PMRA.

3.4.2 Non-Occupational Exposure and Risk Assessment

The non-occupational (residential) risk assessment involves estimating risks to the general population, including youth and children, during or after pesticide application.

The United States Environmental Protection Agency (USEPA) has generated standard default assumptions for developing residential exposure assessments for both applicator and postapplication exposures when chemical- and/or site-specific field data are limited. The assumptions and algorithms may be used in the absence of, or as a supplement to, chemical- and/or site-specific data, and generally result in high-end estimates of exposure. The assumptions and algorithms relevant to the MGK-264 re-evaluation are outlined in the Standard Operating Procedures (SOPs) for Residential Pesticide Exposure Assessments 2012 under "Section 3: Lawns/Turf", "Section 4: Gardens and Trees", "Section 5: Outdoor Fogging/Misting Systems", "Section 7: Indoor Environments" and "Section 8: Treated Pets."

Residential Applicator Exposure and Risk Assessment

A residential applicator refers to an individual (≥ 16 years old) who applies a domestic-class product in or around homes or directly to animals. For MGK-264, the residential applicator would apply the product using a ready-to-use aerosol can, trigger spray bottle, shampoo, roll-on, or dropper bottle. Residential applicators are assumed to be wearing shorts, a short-sleeved shirt, shoes and socks. The residential applicator has the potential for short-term exposure (1 to 30 days) when applying products containing MGK-264.

Calculated MOEs exceeded the target MOE for both dermal and inhalation exposures, and therefore, risks are not of concern. The two exposure routes were not combined since the toxicological point of departures were based on different toxicological effects (see Appendix IV, Table 1).

Residential Postapplication Exposure and Risk Assessment

Residential postapplication exposure occurs when an individual is exposed through dermal, inhalation and/or incidental oral (non-dietary ingestion) routes as a result of being in a residential environment or by contacting an animal that has been previously treated with a pesticide. For MGK-264, the area or animal could have been treated by a residential applicator using a domestic-class product, or by a commercial applicator hired to treat the residential area or animal.

The following postapplication scenarios were assessed for indoor and/or outdoor areas: metered release aerosol space spray applications, space spray applications, and surface spray applications (broadcast, band and spot, and bedbug application). Postapplication exposure from contacting treated animals was also assessed. Multiple applications were not assessed for animals or indoor environments, since exposure on the day of application without any dissipation was assumed for

the entire duration of exposure (for several months). This is considered to be a conservative assumption (that is, resulting in upper bound exposure estimates), when combined with the other dermal exposure inputs in the Residential SOPs.

While exposure may occur for people of all ages, adults (≥16 years old), youth (11 < 16 years old), and children (3 < 6 years old and 1 < 2 years old) were chosen as the index life stages to assess, based on behavioural characteristics and the quality of the available data. Children 2 years old to < 11 years old are not assessed separately, for most scenarios, because their exposure is expected to be less than that of 1 < 2 years old. Children (1 < 2 years) are expected to have a greater exposure because of additional routes of exposure (incidental oral) as well as a greater body surface area (cm^2) to body-weight (kg) ratio.

Postapplication residential exposure to MGK-264 is expected to be intermittent and short-term (1 to 30 days) in duration, with the exception of metered release aerosol space spray applications and bed bug treatment for which it is assumed to result in intermediate-term (30 days to 180 days) exposure, and intermittent short- to long-term (1 to 365 days) exposure, respectively. Adults and youth have the potential for dermal and inhalation exposures, while children (<6 years) have the potential for dermal, inhalation and incidental oral exposures (both hand-to-mouth and object-to-mouth).

For all **dermal exposure scenarios**, the calculated dermal MOEs exceeded the target MOE for all age groups, and therefore, risks are not of concern (see Appendix IV, Tables 2-10).

For **inhalation exposure scenarios in indoor environments**, estimates of exposure are specified in the 2012 USEPA Residential SOPs for both aerosol and vapours. Aerosols are a spray of fine particles, typically present after space spray applications, which tend to settle out of the air after a certain period of time. Vapours occur when the pesticide volatilizes from a surface after application and can occur from all types of pesticide application. For aerosols, inhalation target MOEs were not met until two hours after space spray applications (see Appendix IV, Table 11). For vapours, the calculated inhalation MOEs exceeded the target MOE for most scenarios (see Appendix IV, Tables 12-13, 15), with the exception of indoor dust application, indoor metered release aerosol space spray application, indoor space spray applications at some application rates, and indoor broadcast application for fleas, ticks and carpet beetles using certain domestic-class products.

Inhalation exposure in outdoor environments is expected to be low based on the low vapour pressure of MGK-264 and dilution of any potential airborne concentration with the large airspace outside. For outdoor mosquito abatement, potential inhalation exposure to aerosols is close to the target MOE and, therefore, given the conservative assumptions (that is, resulting in upper bound exposure estimates), risks are not expected to be of concern (see Appendix IV, Table 14).

Incidental oral exposure occurs when pesticide residues are transferred to the hands of children playing on treated surfaces or with treated animals, and are subsequently ingested as a result of hand-to-mouth transfer.

Residues can also be transferred to a child's toy and subsequently ingested as a result of object-to-mouth transfer. Incidental oral exposures from indoor hard surface or carpet applications are considered to be similar to, or have higher exposure, than from mattress applications. For incidental oral exposure scenarios, calculated MOEs exceeded the target MOE, and therefore, risks are not of concern (see Appendix IV, Tables 16-25).

The following mitigation measures are proposed to address the potential risks of concern associated with inhalation exposure as a result of entering residential areas previously treated with products containing MGK-264.

For domestic-class products:

- Cancellation of dust products
- Cancellation of aerosol products for use as a metered release spray
- Cancellation of space spray uses for aerosol products
- Maximum guarantee limited to 0.4% MGK-264 for aerosol products registered for indoor treatment of fleas, ticks, and carpet beetles

For commercial-class products:

- Maximum space spray application rate limited to 0.055 g a.i./m^3 for liquid formulations in certain residential areas (dwellings such as houses, apartments, or in guest rooms of hotels and motels)
- Maximum guarantee limited to 3.3% MGK-264 for aerosol products for use as a metered release space spray
- Prohibit aerosol products for use as a metered release space spray in the following residential areas: dwellings such as houses, apartments, or in rooms attached to dwellings (such as garage, basement), schools, daycare centers, children's hospital wards, guest rooms of hotels, motels, and resorts, or any area where young children may spend more than four hours in a day.
- Entry into treated sites in both residential and commercial areas following an indoor space spray application must not occur until two hours after application. The commercial applicator is responsible for notifying workers, the homeowner and others of this requirement.

In order to retain products that need to be reformulated, registrants would be required to provide a scientific rationale and/or efficacy data to demonstrate that the insecticidal efficacy of their products is not impacted at the reduced MGK-264 guarantee.

3.4.3 Occupational Exposure and Risk Assessment

Workers can be exposed to MGK-264 while handling the pesticide during the application process, when entering a treated area to conduct activities, and when contacting previously treated animals.

Handler Exposure and Risk Assessment

For commercial-class products, there are potential exposures to mixers, loaders and applicators (M/L/As). The following scenarios were assessed:

- Mixing/loading of liquids for automatic stationary foggers/mistblowers and stationary ULV aerosol generators/mechanical aerosol generators (space spray) for dwellings (indoor); commercial, institutional and industrial areas (indoor); and mosquito abatement
- Aerosol application for agricultural premises; kennels; dwellings (indoor and outdoor); commercial, institutional and industrial areas (indoor and outdoor); mosquito abatement; and pets
- Mixing/loading and applying using handheld sprayers (mechanically pressurized handwand, backpack, manually pressurized handwand, mechanical aerosol generator) for outdoor environments: dwellings; commercial, institutional and industrial areas; and mosquito abatement
- Mixing/loading and applying using handheld sprayers (manually pressurized handwand, ULV aerosol generators/mechanical aerosol generators (surface spray)) for indoor environments: agricultural premises; kennels; dwellings; and commercial, institutional and industrial areas
- Mixing/loading and applying using handheld foggers/mistblowers and ULV aerosol generators/mechanical aerosol generators (space spray) for dwellings (indoor); commercial, institutional and industrial areas (indoor); and mosquito abatement
- Mixing/loading and applying using truck mounted equipment for mosquito abatement
- Trigger pump sprayer application for horses and ponies, and pets
- Wipe-on application for horses and ponies
- Shampoo application for pets
- Dropper bottle application for pets

Commercial applicators can apply MGK-264 to many different types of use sites to control a variety of pests. Therefore, their exposure would be intermittent long-term ($\geq$ 6 months).

The PMRA estimated handler exposure based on different levels of personal protective equipment (PPE):

- Baseline PPE: Long pants, long-sleeved shirt. Chemical-resistant gloves were also included for some types of application equipment.
- Chemical Resistant Headgear. Chemical resistant headgear that covers the neck (for example, Sou'Wester hat, rain hat).
- Respirator. A respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides.

No appropriate chemical-specific handler exposure data were available for MGK-264. Therefore, dermal and inhalation exposures were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 and the Agricultural Handlers Exposure Task Force (AHETF). Data from the USEPA Residential SOPs (2012) were also used for application equipment not included in PHED or AHETF. The PHED is a compilation of generic mixer/loader/applicator passive dosimetry data with associated software which facilitates the generation of scenario-

specific exposure estimates based on formulation type, application equipment, mix/load systems and level of PPE. The open cab airblast scenario from AHETF was used in the risk assessment. In most cases, PHED did not contain appropriate data sets to estimate exposure to workers wearing a respirator. This was estimated by incorporating a 90% protection factor for a respirator into the unit exposure values, where applicable. Inhalation exposures were based on light inhalation rates (17 L/min) except for backpack applicator scenarios, which were based on moderate inhalation rates (27 L/min).

For **commercial space spray application using handheld foggers/mistblowers and handheld ULV aerosol generators/mechanical aerosol generators**, measured exposure data are not available. As such, it is proposed to prohibit this application equipment on the labels for space sprays.

For **commercial indoor surface spray application using handheld equipment** (manually pressurized handwands, ULV aerosol generators/mechanical aerosol generators), the PHED wettable powder low pressure handwand scenario was used. Although the products containing MGK-264 are formulated as liquids, it was considered appropriate to use this surrogate scenario, since it is based on studies monitoring commercial indoor pesticide application in residential areas and is more reflective of the exposure potential during indoor application than other liquid PHED scenarios that are based on studies monitoring application in agricultural environments.

Calculated dermal and inhalation MOEs for M/L/As exceeded the target MOE for most scenarios at baseline PPE, and therefore, are not of concern. Target MOEs for applicators using truck-mounted sprayers are not of concern when an enclosed truck cab (windows up) and chemical-resistant gloves were worn. Application using handheld equipment exceeded the target MOEs when chemical-resistant gloves were worn and a respirator was used when applying indoors.

Exposures for the dermal and inhalation routes were not combined for MGK-264 as the toxicological points for departure for these routes were based on different toxicological effects.

The results of the mixer/loader and applicator assessment are presented in Appendix V, Table 1.

Postapplication Worker Exposure and Risk Assessment

Potential occupational dermal and inhalation postapplication scenarios include workers entering treated areas in the following sites:

- Hotels and motels
- Nursing homes and hospitals
- Commercial and public buildings, campgrounds, daycare centers, hospitals, nursing homes, funeral homes, motels, hotels, lodges, resorts, schools, stores, and warehouses
- Food transportation vehicles, buses, trains, ships and trucks
- Food handling and service establishments such as supermarkets, bottling plants, kitchens, meat packing plants, and restaurants
- Pet kennels
- Dairies, farms, livestock housing, including poultry houses

Data were not available to assess indoor postapplication exposures to workers. However, postapplication exposure assessments for residential (non-occupational) areas are considered to be representative for non-residential areas. This assumption is based on the duration and degree of contact with treated surfaces, which is assumed to be greater in residential areas.

No risks of concern were identified for workers entering treated sites for the current uses provided that workers do not enter the treated site until two hours after space spray application (see non-occupational risk assessment).

3.5 Aggregate Exposure and Risk Assessment

Aggregate exposure is the total exposure to a single pesticide that may occur from food, drinking water, residential, and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation).

3.5.1 Toxicology Endpoint Selection for Aggregate Risk Assessment

For **short-term aggregate** risk assessment (general population, including pregnant women, infants and children), the selected toxicological endpoint is liver toxicity. For oral exposure, the rat 2-generation toxicity study was selected. Increased liver weights and liver pathology were observed at the LOAEL of 137 mg/kg bw/day.

For dermal exposure, the rat 21-day dermal toxicity study was selected in which a NOAEL of 1000 mg/kg bw/day (limit dose) was identified. The study did examine liver parameters for evidence of toxicity. A marginal, non-adverse, increased liver weight in the absence of histopathology or clinical chemistry changes related to liver toxicity was noted at the NOAEL.

For inhalation exposure, although increased extramedullary hematopoiesis in liver was noted in the 90-day inhalation study at 0.4 mg/L (25 mg/kg bw/day), this was not considered a hepatotoxic effect. No other indicators of liver toxicity were noted in the study. Thus, inhalation exposure was not aggregated as no common toxicological endpoint was identified.

The target MOE is 100 for the oral and dermal routes of exposure. This target MOE includes a 10-fold uncertainty factor for interspecies extrapolation and a 10-fold uncertainty factor for intra-species variability. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

For **intermediate-term aggregate** risk assessment (general population, including pregnant women, infants and children), the common toxicological endpoint for aggregation was liver toxicity. For oral exposure, the rat 2-generation reproductive study with a parental NOAEL of 33 mg/kg bw/day was selected. Increased liver weights and liver pathology were observed at the LOAEL of 137 mg/kg bw/day.

For dermal exposure, the 21-day dermal study was selected in which a NOAEL of 1000 mg/kg bw/day (limit dose) was identified. The study did examine liver parameters for evidence of toxicity. A marginal, non-adverse, increased liver weight in the absence of histopathology or

clinical chemistry changes related to liver toxicity was noted at the NOAEL. In a rabbit 90-day dermal toxicity study, there was no indication of effects in the liver at the highest dose tested (100 mg/kg); however, higher doses could not be used due to excessive irritation of the skin.

As discussed for the short-term aggregate scenario, inhalation exposure was not aggregated as there was no common toxicological endpoint.

The target MOE is 300, consisting of the standard uncertainty factors of 10-fold for inter-species extrapolation, 10-fold for intra-species variability, and a 3-fold factor for extrapolation from short- to intermediate-term exposure. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

For **long-term aggregate risk assessment** (general population including pregnant women, infants and children), the selected toxicological endpoint was liver toxicity. For both oral and dermal exposure, the 1-year toxicity study in dogs with a NOAEL of 7.4 mg/kg bw/day was selected; increased liver weights and liver pathology were observed at the LOAEL of 33 mg/kg bw/day. For both oral and dermal routes of exposure, the target MOE is 100, consisting of a 10-fold uncertainty factor for inter-species extrapolation and a 10-fold uncertainty factor for intra-species variability. The *Pest Control Products Act* factor was reduced to 1-fold as discussed in the *Pest Control Products Act* Hazard Characterization section.

3.5.2 Residential, Non-Occupational and Dietary Aggregate Exposure and Risk Assessment

In an aggregate risk assessment, the combined potential risk associated with food, drinking water and various residential exposure pathways is assessed. A major consideration is the likelihood of co-occurrence of exposures. Additionally, only exposures from routes that share common toxicological points of departure are aggregated. As such, only exposures from dermal and oral routes were aggregated for MGK-264.

Scenarios which did not have risks of concern were aggregated to determine whether aggregation of exposures would result in risks of concern. Aggregate assessments were conducted for various populations as follows: children (1<2 years old), since they could have both incidental oral exposure and dermal exposure following application in residential areas and to animals, as well as dietary exposure; adults, since they could have both applicator and postapplication dermal exposure, as well as dietary exposure; older children (6<11 years old) and youth, as required, as they could have dermal exposure following application in residential areas and to animals, as well as dietary exposure.

The following scenarios were aggregated:

Indoor residential Areas

- Children (1<2 years old): Short-term dermal exposure from hard or soft surfaces, and chronic food exposure, as well as hand-to-mouth exposure

- Children (1<2 years old): Intermediate-term dermal exposure from hard or soft surfaces following metered release spray, and chronic food exposure, as well as hand-to-mouth exposure
- Children (1<2 years old): Long-term dermal exposure from hard or soft surfaces following bed bug treatment, and chronic food exposure, as well as hand-to-mouth exposure
- Adults: Short-term dermal exposure from application of domestic class products and dermal exposure from hard or soft surfaces, and chronic food exposure
- Adults: Intermediate-term dermal exposure from hard or soft surfaces following metered release spray, and chronic food exposure
- Adults: Long-term dermal exposure from hard or soft surfaces following bed bug treatment, and chronic food exposure

Lawns and Turf
- Children (1<2 years old): Short-term dermal exposure from lawns/turf and chronic food exposure, as well as hand-to-mouth exposure
- Adults: Short-term dermal exposure from application of domestic class products and dermal exposure from lawns/turf, and chronic food exposure for adults

Gardens and Trees
- Children (6<11 years old): Short-term dermal exposure from gardens and trees and chronic food exposure
- Adults: Short-term dermal exposure from application of domestic class products and dermal exposure from gardens and trees, and chronic food exposure for adults.

Treated Pets
- Children (1<2 years old): Short-term dermal exposure from contacting treated pets and chronic food exposure, as well as hand-to-mouth exposure for children (1< 2 years old).
- Adults: Short-term dermal exposure from application of domestic class products and dermal exposure from contacting treated pets, and chronic food exposure for adults.

Calculated aggregate MOEs exceeded the target MOE and calculated Aggregate Risk Indexes (ARIs) were greater than one and, therefore, are not of concern (see Appendix VI, Tables 1-4).

3.6 Cumulative Assessment

The *Pest Control Products Act* requires the Agency to consider the cumulative effects of pest control products that have a common mechanism of toxicity. MGK-264 is an insecticide synergist, which lacks pesticidal effects, but enhances the pesticidal properties of some other pesticides. MGK-264 does not appear to have a common mechanism of toxicity with other pesticides and does not appear to produce a toxic metabolite produced by other substances. A cumulative assessment is therefore not required.

4.0 Environmental Assessment

4.1 Fate and Behaviour in the Environment

MGK-264 is released into the environment by entering the air, when used as a synergist with an insecticide. It can be applied as either as an ultra-low volume (ULV) spray for mosquito abatement, or as an outdoor pressurized spray from a can around homes and commercial, institutional and industrial areas.

Minimal environmental exposure is expected when MGK-264 is applied using a pressurized can around homes and commercial, institutional and industrial areas. ULV sprays enter the air as a fine mist of droplets that float on the air currents to kill adult mosquitoes that come into contact with them. ULV sprays are done when environmental conditions ensure desirable product movement. MGK-264 degrades rapidly in the air (half-life of approximately 1.4 hour) by a chemical reaction with ozone and hydroxyl radicals that occur naturally in air. Consequently, MGK-264 applied by ULV spray is not expected to undergo long range transport in the atmosphere. It is unlikely that MGK-264 applied as fine aerosol droplets would reach soil or water before evaporating or being degraded. There is potential for limited amounts of MGK-264 to reach soil, vegetation and water when applied using pressurized spray cans for domestic uses around homes and on ornamental plants. See Appendix VII, Tables 2-5.

MGK-264 breaks down slowly in soil. The main route of transformation in soil is microbial degradation. Insufficient data were available to fully assess the behaviour of MGK-264 in water, however, as in air, free radical reactions are expected to degrade MGK-264.

MGK-264 is moderately toxic to fish and aquatic invertebrates. Risks of concern for aquatic organisms are not expected due to limited exposure. Currently registered labels advise users to take care not to contaminate sensitive aquatic environments such as sloughs, ponds, prairie potholes, lakes, rivers, streams and wetlands when cleaning and rinsing spraying equipment and containers.

MGK-264 may accumulate in the tissues of organisms but exposure is expected to be limited due to its methods of application, and the rapid degradation in air.

4.2 Environmental Risk Characterization

The environmental risk assessment integrates the environmental exposure and ecotoxicology information to estimate the potential for adverse effects on non-target species. This integration is achieved by comparing exposure concentrations with concentrations at which adverse effects occur. Estimated environmental exposure concentrations (EECs) are concentrations of pesticide in various environmental media, such as food, water, soil and air. The EECs are estimated using standard models which take into consideration the application rate(s), chemical properties and environmental fate properties, including the dissipation of the pesticide between applications.

Ecotoxicology information includes acute and chronic toxicity data for various organisms or groups of organisms from both terrestrial and aquatic habitats including invertebrates, vertebrates, and plants. Toxicity endpoints used in risk assessments may be adjusted to account for potential differences in species sensitivity as well as varying protection goals (in other words, protection at the community, population, or individual level).

Initially, a screening level risk assessment is performed to identify pesticides and/or specific uses that do not pose a risk to non-target organisms, and to identify those groups of organisms for which there may be a potential risk. The screening level risk assessment uses simple methods, conservative exposure scenarios (for example, direct application at a maximum cumulative application rate) and sensitive toxicity endpoints. A risk quotient (RQ) is calculated by dividing the exposure estimate by an appropriate toxicity value (RQ = exposure/toxicity), and the RQ is then compared to the level of concern (LOC). If the screening level RQ is below the LOC, the risk is considered negligible and no further risk characterization is necessary. If the screening level RQ is equal to or greater than the LOC, then a refined risk assessment is performed to further characterize the risk.

A refined assessment takes into consideration more realistic exposure scenarios (such as drift to non-target habitats) and might consider different toxicity endpoints. Refinements may include further characterization of risk based on exposure modelling, monitoring data, results from field or mesocosm studies, and probabilistic risk assessment methods. Refinements to the risk assessment may continue until the risk is adequately characterized or no further refinements are possible.

4.2.1 Risks to Terrestrial Organisms

A summary of terrestrial toxicity data for MGK-264 is presented in Appendix VII, Tables 6-10. For assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following exposure to MGK-264 (Appendix VII, Table 13).

No data were provided to determine potential effects of MGK-264 on insects, and as such, effects are unknown. Despite this, risks to insects due to MGK-264 are expected to be low. For example, exposure to bees that may be present in the fogging areas is minimized since mosquito spray programs are conducted at night, when the bees are not active. Some individuals of non-target insects and other arthropods, that are present in the residential areas and that are active at spraying times, may be affected. However, it is expected that the effects on the populations will not be permanent due to recolonization from rural unsprayed areas.

The terrestrial assessment took into account that MGK-264 may be ingested by birds or mammals who may feed on insects or on plants that have been sprayed using pressurized spray cans in outdoor residential uses and on outdoor ornamental plants. A risk assessment was conducted considering these potential routes of exposure and it was determined that MGK-264 presents negligible risk to birds and mammals (Appendix VII, Tables 14-15). Toxicity information was available for birds and mammals only.

MGK-264 is used in combination with insecticides for adult mosquito control and is applied as an ULV spray where it will either degrade rapidly due to reactions with hydroxyl radicals or evaporation of suspended droplets. As such, very little if any MGK-264 is expected to reach soil or plant surfaces. Exposure to terrestrial organisms from sprays applied by homeowners to outdoor surfaces and ornamental plants are limited in area and expected to pose limited potential for exposure.

4.2.2 Risks to Aquatic Organisms

A summary of aquatic toxicity data for MGK-264 is presented in Appendix VII, Tables 6, 11 and 12. For assessment of risk, toxicity endpoints chosen from the most sensitive species were used as surrogates for the wide range of species that can be potentially exposed following exposure to MGK-264. Toxicity information was available for freshwater fish and invertebrates only. MGK-264 is used in combination with insecticides for adult mosquito control and is applied as an ULV spray where it will either degrade rapidly due to reactions with hydroxyl radicals or evaporation of suspended droplets. As such, very little if any MGK-264 is expected to reach water. Exposure to aquatic organisms from sprays applied by homeowners to outdoor surfaces and ornamental plants are limited in area and expected to pose limited potential for exposure through surface runoff to water bodies.

A conservative risk assessment was conducted assuming that 100% of ULV spray applications would be deposited to water surfaces (Appendix VII, Tables 16-18). The resulting LOC was not exceeded for freshwater aquatic invertebrates, fresh, cold-water fish or amphibians. No data were available for aquatic plants or algae. These data are not required due to negligible exposure. Since MGK-264 is only present as a co-formulant with insecticides and not registered for use on its own, buffer zones that may appear on some product labels are related to the insecticide component of the formulation rather than MGK-264.

5.0 Value

MGK-264 is an insecticide synergist that is used in co-formulated products containing active ingredients belonging to synthetic pyrethroids and pyrethrins. The synergist enhances the pesticidal properties of the other insecticides, thus reducing the amount of these insecticides required for pest control. MGK-264 is registered to manage a wide spectrum of insect pests in stored food and feed, structures, companion animals, human habitat and recreational areas, human skin, clothing and proximal sites, and residential outdoors.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The Toxic Substances Management Policy (TSMP) is a federal government policy developed to provide direction on the management of substances of concern that are released into the environment. The TSMP calls for the virtual elimination of Track 1 substances, those that meet all four criteria outlined in the policy: in other words, persistent (in air, soil, water and/or sediment), bio-accumulative, primarily a result of human activity and toxic as defined by the *Canadian Environmental Protection Act*.

During the review process, MGK-264 was assessed in accordance with the PMRA's Regulatory Directive DIR99-03[5], and evaluated against the Track 1 criteria. The PMRA has reached the following conclusions:

- MGK-264 does not meet Track 1 criteria. See Appendix VII, Table 19 for comparison with Track 1 criteria. Available fate data indicates that MGK-264 will not persist in air and it does not meet the bioaccumulation criteria. It is expected that the ULV method of spray application for mosquito control and rapid degradation of MGK-264 in air precludes the formation of significant amounts of transformation products.

6.2 Formulants and Contaminants of Health or Environmental Concern

During the review process, contaminants in the technical are compared against the list maintained in the *Canada Gazette*[6]. The list is used as described in the PMRA's Notice of Intent NOI2005-01[7] and is based on existing policies and regulations including: DIR99-03; and DIR2006-02[8], and taking into consideration the Ozone-depleting Substance Regulations, 1998, of the *Canadian Environmental Protection Act* (substances designated under the Montreal Protocol). The PMRA has reached the following conclusions:

- Technical grade MGK-264 does not contain any contaminants of health or environmental concern identified in the *Canada Gazette*.

The use of formulants in registered pest control products is assessed on an ongoing basis through the PMRA formulant initiatives and DIR2006-02.

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5 DIR99-03, *The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*

6 *Canada Gazette*, Part II, Volume 139, Number 24, SI/2005-114 (2005-11-30) pages 2641–2643: *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern and in the order amending this list* in the Canada Gazette, Part II, Volume 142, Number 13, SI/2008-67 (2008-06-25) pages 1611-1613. Part 1 *Formulants of Health or Environmental Concern*, Part 2 *Formulants of Health or Environmental Concern that are Allergens Known to Cause Anaphylactic-Type Reactions* and Part 3 *Contaminants of Health or Environmental Concern*.

7 NOI2005-01, *List of Pest Control Product Formulants and Contaminants of Health or Environmental Concern* under the *New Pest Control Products Act*.

8 DIR2016-02, *PMRA Formulants Policy*

7.0 Incident Reports

Since 26 April 2007, registrants have been required by law to report pesticide incidents, including adverse effects to health and the environment, to the PMRA. In addition, the general public, medical community, government and non-governmental organizations are able to report pesticide incidents directly to the PMRA. Information on the reporting of incidents can be found on the Pesticides and Pest Management portion of the Canada.ca website.

As of 28 June 2017, 147 human incidents and 845 domestic animal incidents were reported for the synergist MGK-264. All of these incidents involved other active ingredients in addition to the synergist MGK-264. None of these incidents were considered to be related to exposure to MGK-264. Therefore, no concerns related to human or domestic animal health were identified for MGK-264 based on the incident reporting information. There have been no environmental incidents involving MGK-264 reported to the PMRA. As such, no additional measures based on incident reports involving MGK-264 were required.

8.0 Proposed Re-evaluation Decision

The PMRA proposes that most products containing MGK-264 for use and sale in Canada are acceptable for continued registration. Based on the evaluation of currently available scientific information, mitigation measures are proposed to further protect human health, including the cancellation of certain domestic-class products and uses. Additional data related to value would be required for products that need to be reformulated.

The labels of Canadian end-use product must be amended to include the label statements listed in Appendix VIII.

8.1 Proposed Regulatory Action Related to Human Health

8.1.1 Proposed Mitigation Related to Toxicology

No mitigation measures are proposed.

8.1.2 Proposed Mitigation Related to Dietary Exposure

To protect consumers from potential residues in or on food, the following measures are proposed:

- All commercial-class labels to include the statement: "Application on livestock intended for food production is prohibited."
- All labels to include the statement: "Cover or remove exposed food and food handling surfaces prior to application."

8.1.3 Proposed Mitigation Related to Occupational and Residential Exposure

To protect residential applicators and those entering treated residential and commercial areas, the following measures are proposed:

For domestic-class products:

- Cancellation of dust products
- Cancellation of aerosol products for use as a metered release space spray
- Cancellation of space spray uses from aerosol product labels
- Maximum guarantee limited to 0.4% MGK-264 for aerosol products registered for indoor treatment of fleas, ticks, and carpet beetles
- Label directions to include definition of broadcast and spot/band treatment, if similar or more restrictive instructions are not already present on the label.

For commercial-class products:

- Maximum space spray application rate limited to 0.055 g a.i./m^3 for liquid formulations in certain residential areas (dwellings, such as houses, apartments, or in guest rooms of hotels and motels)
- Maximum guarantee limited to 3.3% MGK-264 for aerosol products for use as a metered release space spray
- Prohibit aerosol products for use as a metered release space spray in the following residential areas: dwellings such as houses, apartments, or in rooms attached to dwellings (for example, garage, basement), schools, daycare centers, children's hospital wards, guest rooms of hotels, motels, and resorts, or any area where children may spend more than four hours in a day
- Entry into treated sites in both residential and commercial areas following an indoor space spray application must not occur until two hours after application. The commercial applicator is responsible for notifying workers, the homeowner and others of this requirement. This is not required for metered-release aerosol products.
- Label directions to include definition of indoor broadcast and spot/band treatment, if similar or more restrictive instructions are not already present on the label.

To protect mixer/loader/applicators, additional protective equipment is proposed:

- Long-sleeved shirt and long pants for all commercial applicators
- Chemical-resistant gloves for handheld application, as well as a respirator if applying in indoor environments
- An enclosed truck cab (closed windows) and chemical-resistant gloves for truck-mounted sprayer application
- Prohibit the use of handheld foggers/mistblowers
- Prohibit the use of handheld ULV aerosol generators/mechanical aerosol generators for space sprays.

To protect bystanders from spray drift, the following measures are proposed:

- Statement to promote best management practices to minimize human exposure from spray drift or spray residues resulting from drift in non-target areas.

8.1.4 Residue Definition for Risk Assessment and Enforcement

As MGK-264 is not registered for use on agricultural growing crops, and application to livestock intended for food production is not supported by the registrant, plant and livestock metabolism studies were not required.

Metabolism studies in rat (see section 3.1) and environmental fate studies (see section 4.0) indicate that MGK-264 is a stable compound (absorbed and excreted with little retention of metabolites, stable to abiotic degradation and persistent in soil with a half-life of approximately one year). Therefore, MGK-264 is proposed as the residue definition for risk assessment and enforcement purposes.

8.2 Other Requirements

To protect human health, the PMRA proposes to limit the maximum guarantee for certain commercial- and domestic-class products (see section 3.4.2 for details). In order to retain products that need to be reformulated, registrants would be required to provide a scientific rationale and/or efficacy data to demonstrate that the insecticidal efficacy of their products is not impacted at the reduced MGK-264 guarantee.

List of Abbreviations

↑	increased
↓	decreased
♀	females
♂	males
abs	absolute
a.i.	active ingredient
ADI	acceptable daily intake
AHETF	Agricultural Handler Exposure Task Force
ALP	alkaline phosphatase
AR	applied radioactivity
ARfD	acute reference dose
ARI	aggregate risk index
ARTF	Agricultural Re-Entry Task Force
ATPD	area treated per day
BUN	blood urea nitrogen
bw	body weight
bwg	body weight gain
CAF	composite assessment factor
CAS	Chemical Abstracts Service
CFIA	Canadian Food Inspection Agency
cm	centimetre(s)
CR	chemical resistant
Ctrl	control
d	day
DEEM	Dietary Exposure Evaluation Model
DER	Data Evaluation Record
DFR	dislodgeable foliar residue
DT_{50}	dissipation time to 50%
EC_{50}	effective concentration to 50%
EEC	estimated environmental concentration
EFED	Environmental Fate and Effects Division (USEPA)
fc	food consumption
F1	first generation
F2	second generation
g	gram(s)
GD	gestation day
ha	hectare
hr	hour
IUPAC	International Union of Pure and Applied Chemistry
K_d	adsorption coefficient
kg	kilogram
K_{oc}	organic carbon partition coefficient
K_{ow}	n-octanol/water partition coefficient at 25°C
L	litre(s)
LC_{50}	median lethal concentration

LD_{50}	median lethal dose
LOAEC	lowest observable adverse effect concentration
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
MAS	maximum average score for 24, 48 and 72 hours
max	maximum
mg	milligram(s)
min	minute(s)
mL	millilitre(s)
MOE	margin of exposure
mol	moles
mPa	millipascal(s)
MRID	USEPA's Master Record Identifier Number
MRL	maximum residue limit
NIOSH	National Institute for Occupation Safety and Health
nm	nanometre(s)
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PCPA	*Pest Control Products Act*
PDP	Pesticide Data Program
PHED	Pesticide Handlers Exposure Database
PIS	primary irritation score
PMRA	Pest Management Regulatory Agency
PND	post natal day
PPE	personal protective equipment
ppm	parts per million
rel	relative
RQ	risk quotient
SOP	standard operating procedures
ss	statistically significant
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
UV	Ultraviolet
wk	week
wt	weight

Appendix I Toxicological Information for Health Risk Assessment

Effects are known or assumed to occur in both sexes unless otherwise noted; in such cases, sex-specific effects are separated by semi-colons.

Table 1 Toxicology Profile for MGK-264

Study Type / Animal/ PMRA #	Study Results
Toxicokinetics Oral (gavage) Sprague Dawley CD rats PMRA # 1157176, 1157177, 1157178, 1157179, 1157200, 1157201	Absorption: MGK-264 radiolabelled in either norbornene-2, 3-^{14}C or hexyl-1-^{14}C positions was rapidly absorbed. Blood concentration of ^{14}C for both radiolabels peaked at 4-6 hrs and 6 hrs for ♂ and ♀, respectively. Distribution: Seven days following a radiolabelled dose, for either radiolabel, tissue retention was minimal (< 1%) in all dosing regimens. Highest radioactivity (% of dose) was seen in the intestines, carcass and liver. With a single oral dose (low or high) retention was higher in ♂ compared to ♀. With administration of multiple low doses, both sexes retained comparable residue in tissues. Metabolism: Metabolism was extensive. Unchanged MGK-264 was not found in the urine samples, and appeared only in small amounts in the feces (<2.6 – 5.3%). Four major and some minor metabolites were identified. Major metabolites included carboxylic acids produced by either β- or ω-1 oxidation of the side chain and epoxides which were formed by oxidation of the double bonds of the norbornene ring. A minor product that co-eluted with a major metabolite was also identified as a carboxylic acid with the norbornene ring intact and unoxidized. Several other unidentified minor metabolites comprised less than 10% of administered radioactivity. The proposed metabolic pathway for both radiolables was identical. The half-life of blood radioactivity was 4.2 (♂) and 3.5 hrs (♀) with Norbornene-2, 3-^{14}C labelled MGK-264 and ~8 (♂) and 6 hrs (♀) with Hexyl-1-^{14}C labelled MGK-264. There was a sex difference in quantitative metabolism of MGK-264 for both radiolabels. Females excreted a higher amount of less polar metabolites in the urine, whereas males excreted higher amount of more polar metabolites in the feces. Excretion: Radioactivity in expired air as $^{14}CO_2$ was insignificant (<0.02% of the administered dose). Excretion was rapid. Most administered radioactivity was recovered within the first 24-36 hrs in urine and 36-48 hrs in feces. With single or repeat administration of low doses radiolabeled in either position, ♂ eliminated a comparable amount (44 and 50%) of the dose in urine and feces, respectively. ♀ showed a different pattern with approximately 70% of the dose excreted in the urine and 25% in the feces. Greater urinary elimination (~70%) was observed in both sexes with the high dose administration.
Oral Outbred SD rats PMRA # 1157160, 1167333, 1238003	LD_{50} = 4.98 g/kg bw (♂/♀) **Low acute toxicity** ≥ 3 g/kg bw: mortality, ruffled and lethargic appearance, nasal/ocular or oral discharge

Study Type / Animal/ PMRA #	Study Results
Dermal NZW rabbits PMRA # 1188405, 1157158	LD_{50} > 2.0 g/kg bw (♂/♀) **Low acute toxicity** Signs of toxicity: transient diarrhea, no feces or soft stool, skin irritation (erythema and edema) progressed to denuded skin, eschar, fissuring to exfoliation.
Inhalation (whole body) SD rats PMRA # 1157161, 1167325, 1238005	LC_{50} = 4.08 mg/L (♂/♀) **Low acute toxicity** ≥5 mg/L: nasal discharge and wheezing ≥8 mg/L: gasping 9 mg/L: sluggish movement, slight tremors
Eye Irritation NZW rabbits PMRA # 1157158	Maximum average score = 10.7 MAS (1hr) = 10.7 (64/6) MAS (24hrs) = 4.3 (26/6) MAS (48hrs) = 2.3 (14/6) MAS (72hrs) = 1.7 (10/6) **Mildly irritating**
Dermal Irritation NZW rabbits PMRA # 1238007, 1157148, 1167327, 1238008	Primary irritation score = 1.17 PIS (24-72 hrs) = 4.66/4 **Slight ocular irritant**
Dermal Sensitization (Modified Buehler test) - albino guinea pigs PMRA # 1238007, 1157148, 1167327, 1238008	Negative **Not a dermal sensitizer**
Short-Term Toxicity Studies	
90-day oral (dietary) CD-1 mice PMRA # 1157166	**NOAEL = 500 mg/kg bw/day** (for liver effects only) **LOAEL= 1000 mg/kg bw/day**, based on enlarged and discolored liver, biliary stasis; hepatocellular hypertrophy, hepatic discoloration (♂) Only the liver was microscopically examined. No clinical chemistry analysis was performed.
90-day oral (dietary) CD rats PMRA # 1157172	**Supplemental** **≥ 125 mg/kg bw/day**: ↓ fc (♀) **≥ 250 mg/kg bw/day**: ↑ liver weight ↓ bw, ↓ bwg, ↑ BUN (♀) **≥ 500 mg/kg bw/day**: enlarged liver; ↓ bw, ↓ bwg, ↓ fc (♂); ↑ globulins (♀)

Study Type / Animal/ PMRA #	Study Results
61-day dietary Beagle dogs PMRA # 1157186	**Supplemental** **≥ 4 mg/kg bw/day**: ↓ bw ,↑ ALT, ↓ abs heart wt, ↓ heart rel to brain wt,↓ abs spleen wt, ↓ spleen rel to brain wt (♂) **≥ 8 mg/kg bw/day**: ↓ bw,↓ bwg; ↓ abs kidney wt,↓ kidney rel to brain wt (♂) **≥ 34 mg/kg bw/day**: ↓ bw, ↓ bwg; granulated liver (1 dog)(♂); ↑ ALT,↑ ALP, ↓ kidney rel to brain wt (♀)
1-year oral (dietary) Beagle dogs PMRA # 1157163	**NOAEL = 7.4 mg/kg bw/day** **≥7.4 mg/kg bw/day**: (non-adverse):↑ thyroid/parathyroid wt (including relative to brain wt) ♀. **33 mg/kg bw/day**: ↑ liver (including relative to brain) wt, biliary stasis (brown pigment), slight ↑ALP, AST and ALT; hepatocellular hypertrophy 2 dogs (♂); ↓ albumin, mononuclear cell foci in parenchyma of the liver (1 dog) ♀.
21-day dermal Crl:CD®(SD) rat PMRA # 2129798	**Systemic NOAEL = 1000 mg/kg bw/day** based on ↑rel liver weights of 8 -10%; ↑abs. cosinophil count ($p \leq 0.01$) (♂); (non-adverse) **Dermal LOAEL = 300 mg/kg bw/day,** based on skin irritation, ↑hyperplasia of the epidermis and follicular epithelium in all treated groups; ↑ serocellular crust (♀).
7-day dermal (range-finding) NZW rabbits PMRA # 157199	**Supplemental** **≥100 mg/kg bw/day**: erythema and edema in all treated animals **1000 mg/kg bw/day**: severe skin irritation (desquamation and scabbing), slight ↑ incidence of hair loss in the abdominal region (not the application site); firm, discolored and enlarged salivary glands, enlarged pale spleen, yellow nodule in liver (1 rabbit) (♀).
14-day dermal (range-finding) NZW rabbits PMRA # 1157198	**Supplemental** **≥10 mg/kg bw/day**: mild skin irritation **100 mg/kg bw/day**: In 1 rabbit: slight bodyweight loss and ↓food consumption, liquid feces on occasion, pustules, desquamation, and eschar at the application site (♀).
90-day dermal NZW rabbits PMRA # 1157197	**Systemic NOAEL = 100 mg/kg bw/day (HDT)** **Dermal NOAEL = 10 mg/kg/bw** based on dermal irritation.
90-day inhalation SD rats PMRA # 1167329, 1157162	**LOAEC = 0.01 mg/L (~ 1.9 mg/kg bw/day)** **≥ 0.01 mg/L**: nasal discharge, metaplasia/hyperplasia of the pseudostratified columnar epithelium and keratinized metaplastic epithelium of the mucosa in the larynx (no incidences in controls – severity increased with dose); red facial stains (♀) **≥ 0.135 mg/L**: ↑ hyperplasia or hyperkeratosis of stratified squamous epithelium of the larynx mucosa (no full recovery at high dose), ↑ secretion of epithelial intracytoplasmic cosinophilic material in nasoturbinal tissues (comparable to controls after recovery at high dose); ↑ severity of goblet cell hyperplasia in the respiratory epithelium in the nasoturbinal tissues (comparable to controls after recovery at high dose)(♂) **0.4 mg/L**: ↑ severity of sub-acute/chronic inflammation of the mucosa in the larynx (reduced after recovery), ↑ incidence of hypertrophy/hyperplasia of goblet cells in the epithelium lining of the nasopharynx (no increase in severity) (almost completely recovered after the recovery period), ↓ activity during exposure, excessive salivation (first two weeks); moribundity (1 ♂), red facial stains, ↑ extramedullary hematopoiesis in liver (♂),↑ sinus ectasia/cystic dilatation of mediastinal lymph node, ↑ dilated glands of

Study Type / Animal/ PMRA #	Study Results
	stomach mucosa. 2/16 rats with degeneration/atrophy of germinal epithelium in testis (1 of these also had maturation arrest in testis and oligospermia with degenerated seminal product in the epididymis) (♂).
18-month oral (dietary) chronic toxicity/ oncogenicity CD-1 mice PMRA #1157170	**NOAEL = 50 mg/kg bw/day (♂)** **NOAEL = 400 mg/kg bw /day (♀)** **≥400 mg/kg bw/day**: ↓ bw not ss ,↑ liver weights; ↑ calculi in the gallbladder, ↑ liver nodules/masses, biliary stasis (♂) **800 mg/kg bw/day**: hepatocellular hypertrophy (30 vs 1 for ctrl A and 2 for ctrl B) in ♂,6 vs 0 for both ctrl's in ♀); slight ↓ survival (between wks 52-78), ↑ hepatocellular adenomas, ↑ calculi in the liver, ↑ cysts in the liver, ↑ spongiosis hepatitis in the liver, ↑ vacuolar change in the liver, ↑ portal duct proliferation in the liver, ↑ portal mononuclear cell infiltration (♂); ↓ bw (6% of ctrl A and 9 % of ctrl B), ↑ liver nodules, ↑ calculi in the gallbladder (♀) Increased incidence of hepatocellular adenomas in high-dose (♂) and combined adenoma/carcinomas in mid- (♂) and high-dose (♂ and ♀) were observed: Incidence of hepatocellular adenomas: (n=50) ♂: 3, 1, 1, 6, 12**(5.2,13.38%) ♀: 0,0,0,1,2 (0,0,2,4%) Incidence of hepatocellular carcinoma: ♂: 0, 2, 1, 3, 1 (2,2,7,3%) ♀: 0,0,0,0,1 (0,0,0,2%) Incidence of combined hepatocellular adenoma/carcinoma: ♂: 3,3,2,9*,13** ♀: 0,0,0,1,3* for 2 control groups and treated groups. * Statistically significant at $p \leq 0.05$ ** Trend Historical control incidence (range(mean)) (♂) adenoma: 0-18% (9.93%) carcinoma: 0-5% (2.3%) (♀) adenoma: 0-3.33% (0.94%) carcinoma: 0-1.67% (1/745) **Evidence of tumourigenicity.**
24-month oral (dietary) combined chronic toxicity/ oncogenicity Charles River CD rats PMRA # 1157152, 1157149	**NOAEL = 50 mg/kg bw/day** **LOAEL = 150 mg/kg bw/day,** based on ↓ bw near end of study- not ss, ↓ bwg, ↑ hepatocellular hypertrophy, cholangiofibrosis; ↑ tan/white foci in liver (♂); brown pigment in the convoluted tubule epithelium of the kidney, ↑ liver weights (♀) **450 mg/kg bw/day**: ↓ bw, ↓ bwg, ↑ clear kidney cysts, bile stasis, bile duct cyst, ↑ portal bile duct proliferation, spongiosis hepatic; ↑ brown pigment in the convoluted tubule epithelium of the kidney, clear cell altered foci, eosinophilic altered foci, (♂); ↑tan/white foci in liver, ↓ Hb, ↓ Hct, slight changes in MCV, MCH, and MCHC, ↑ BUN, ↑ cholesterol,↑ total protein, ↑ globulin (♀). There was a statistically significant (Peto's test) ↑ incidence of thyroid follicular cell adenomas in mid- and high-dose (♂) as well as and in the combined adenomas /carcinomas for the high-dose (♂): Follicular adenomas ♂: 3,4,5*,6* (3,7,9,11%)(n=60); follicular carcinomas ♂:2,2,1,3 (3,5,3,7%). Combined follicular adenomas/carcinomas ♂: 5,6,6,9** for control and treated groups, respectively. * Statistically significant at $p \leq 0.05$;** Statistically significant at $p \leq 0.01$. Historical control: adenoma 1.7-6 %. **Evidence of tumourigenicity.**

Study Type / Animal/ PMRA #	Study Results
Developmental/Reproductive Toxicity Studies	
Developmental toxicity (gavage) range-finding study CD rats PMRA # 1157168, 1238009	**Supplemental** <u>Maternal toxicity:</u> **≥500 mg/kg bw/day**: moribundity (1animal GD 11). ↓ motor activity and bodyweight gain, ↑ dilated pupils, ↑ sensitivity to external stimuli. **≥1000 mg/kg bw/day**: bw loss (GD 6-9) **2000 mg/kg bw/day**: mortality (GD 9 and 11), moribundity,↑ early resorptions, ↑post-implantation loss, ↓live fetuses, ↑salivation. <u>Developmental toxicity:</u> **2000 mg/kg bw/day**: ↑ early resorptions, ↓live fetuses.
Developmental toxicity (gavage) CD rats PMRA # 1157164, 1238011	<u>Maternal toxicity:</u> **NOAEL = 300 mg/kg bw/day** **LOAEL = 1000 mg/kg bw/day**, based on incidence of post-dosing salivation, ↓ bw (GD 6-9 and 6-16), mortality (1 dam on GD 10), reduced pregnancy rate. <u>Developmental toxicity:</u> **NOAEL = 1000 mg/kg bw/day** No developmental effects were noted. **No evidence of treatment-related developmental toxicity or sensitivity of the young.**
Developmental toxicity (gavage) range-finding study NZW rabbits PMRA # 1157169	**Supplemental** **≥ 300 mg/kg bw/day**: one moribundity (GD-28), three abortions (26-28 days), ↓ bw (GD 7-19) and all the gestation period (0-29), the only surviving dam had no viable fetuses (post-implantation loss). Clinical signs: No stool or soft stool, red fluid in the pan, stained hair coat in anogenital area, abortion, convulsions, decreased or lack of activity, loss of righting reflex, ataxia and rattled or labored breathing, moribundity, inflammation, ulceration and/or necrosis of the stomach mucosa. **≥ 600 mg/kg bw/day**: two deaths, two abortions (GD's 22,28), ↓ bw all GDs, the only surviving dam had no viable fetuses (post-implantation loss) **≥ 900 mg/kg bw/day**: complete mortality, ↓ bw prior to death. High pre-implantation loss (53%) in the control group Different dose volumes were used for gavage dosing.
Developmental toxicity (gavage) NZW rabbits PMRA # 1157167	**Maternal and developmental NOAEL = 100 mg/kg bw/day** No maternal or fetal treatment-related effects. **No evidence of treatment-related developmental toxicity or sensitivity of the young.**
4-week dose reproductive toxicity range finding (dietary) for PMRA #2332126 Wistar rats PMRA# 2129797	**Supplemental** **≥ 51/66 mg/kg bw/day**: A minimal to moderate lobular fat accumulation demonstrated by the ORO-stain. **≥ 102/106 mg/kg bw/day**: lobular fat accumulation; enlargement and distinct lobulation of the liver, a minimal to moderate hypertrophy and eosinophilic cytoplasmic change of the centrilobular hepatocytes (♂) and both sexes at the high dose; ↓fc (♀)

Study Type / Animal/ PMRA #	Study Results
	997 /1269 mg/kg bw/day: ↓ body weight,↓ weight gain (week-1), ↑fc, cholestasis of the intrahepatic bile ducts with a minimal to slight pericholangiolar mononuclear cell infiltration, bile duct proliferation and signs of degeneration of the bile duct epithelium.
2-generation reproductive toxicity (dietary) (1990) COBS rats PMRA #1157171	Parental toxicity: **NOAEL = 62 /76 mg/kg bw/day (♂ / ♀)** **≥121/141 mg/kg bw/day**: hepatocyte hypertrophy ♂ F1 and ♀ (F1); ↓fc (P, F_1) (♀) Offspring toxicity: **LOAEL = 76 mg/kg bw/day** **≥76 mg/kg bw/day:**↓ pup bw PND 14-28 (no clear dose response) **≥141 mg/kg bw/day**: ↓ pup bw PND 7-28 Reproductive toxicity: **NOAEL = 121 mg/kg bw/day** **622/746 mg/kg bw/day**: ↓ gestation index, ↑ copulatory interval at 2nd mating (P only) **No evidence of sensitivity of the young.**
2-generation reproductive toxicity (dietary) (2009) Wistar rats PMRA # 2332126	Parental toxicity: **NOAEL = 33/51 mg/kg bw/day(♂ / ♀)** **≥ 1600 ppm:** ↑ brownish pigment in kidney (P and/or F1);↑ liver hypertrophy and/or cosinophilic cytoplasmic changes of centrilobular hepatocytes (P and F1), ↑ periportal/centrilobular fat storage (P and F1), thyroid gland follicular cell hypertrophy and/or colloidal alterations (P and F1)(♂); ↓ bw on GD 20, ↑fc (GD 14-20) (F1 2-nd mating), ↑ liver wt (P and F1), distinct lobulation of the liver (♀), ↑ kidney wt, ↑ periportal hypertrophy (P) (♀) Offspring Toxicity: **NOAEL = 212 mg/kg bw/day** **6400 ppm:** ↓ mean litter size F1 pups (due to ↓ number implantation sites), ↑ deaths on PND (5-21) F1 pups, ↑ thin or small pups; pronounced ↓ pup wt (F1 and F2), delayed vaginal opening (F1)(4 days); Reproductive Toxicity: **NOAEL = 137/212 mg/kg bw/day(♂ / ♀)** **6400 ppm**: ↓ ovary wt (P1),↓ number implantation sites (P1), altered luteneization of corpora lutea (P1 and F1) and ↑ duration of met-/diestrus cycle in F1, ↑ wt of seminal vesicle/coagulating glands (P) **No evidence of sensitivity of the young.**
Genotoxicity	
Unscheduled DNA synthesis - primary rat hepatocytes PMRA # 1157155	Negative

Study Type / Animal/ PMRA #	Study Results
Unscheduled DNA synthesis - primary rat hepatocytes PMRA #2129804	Negative
Salmonella/Mammalian microsome plate incorporation - *Salmonella typhimurium* TA98, 100, 1535, 1537, 1538 (Ames test with a confirmatory assay) PMRA #2129803	Negative (± S-9)
Chromosome aberration assay - Chinese hamster ovary cells PMRA #1157153	Negative (± S-9)
Lymphoma mutagenesis assay - L5178Y TK$^{+/-}$ mouse lymphoma cells PMRA #1157154	Without S-9: Equivocal (2 fold increase in mutant frequency at 0.012-0.013 µl/mL with less than 10 % total growth, but no dose-response) With S-9: Negative

Table 2 Toxicology Reference Values for MGK-264

Exposure Scenario	Study	Point of Departure and Endpoint	CAF[1] or Target MOE
Acute dietary (All populations)	Rabbit developmental toxicity (range finding)	NOAEL = 100 mg/kg bw/day ↓bwg during the first few days (GD 6-9) of dosing at 300 mg/kg bw/day	100
	ARfD = 1 mg/kg bw		
Repeated dietary (All populations)	Dog 1- year dietary	NOAEL = 7.4 mg/kg bw/day Liver toxicity at 33 mg/kg bw/day	100
	ADI = 0.07 mg/kg bw/day		
Short-term dermal	Rat 21-day dermal	NOAEL = 1000 mg/kg bw/day (HDT)	100
Intermediate –term dermal	Rabbit 90-day dermal	NOAEL = 100 mg/kg bw/day (HDT)	100
Long-term dermal[2]	Dog 1 year dietary study	NOAEL = 7.4 mg/kg bw/day Liver toxicity at 33 mg/kg bw/day	100
Short- and intermediate-term inhalation	Rat 90- day inhalation	LOAEC = 0.01 mg/L (1.9 mg/kg bw/day) Metaplasia/hyperplasia and keratinization of the larynx epithelium	300
Long-term inhalation	Rat 90- day inhalation	LOAEC = 0.01 mg/L (1.9 mg/kg bw/day) Metaplasia/hyperplasia and keratinization of the larynx epithelium	1000

Short - and intermediate-term incidental (non-dietary) oral ingestion	Rat 2-generation reproduction (2009)	Parental NOAEL = 33 mg/kg bw/day Liver toxicity at 137 mg/kg bw/day	100
Aggregate risk: short-term	Oral: 2-generation rat reproduction Dermal: 21-day rat dermal Inhalation	Parental NOAEL= 33 mg/kg bw/day Liver toxicity at 137 mg/kg bw/day NOAEL= 1000 mg/kg bw/day No endpoint for aggregation	100 100
Aggregate risk: intermediate-term	Oral: 2-generation rat reproduction Dermal: 21-day rat dermal Inhalation	Parental NOAEL = 33 mg/kg bw/day Liver toxicity at 137 mg/kg bw/day NOAEL = 1000 mg/kg bw/day (HDT) No endpoint for aggregation	100 300
Aggregate risk: long-term	For both oral and dermal Dog 1-year dietary	NOAEL = 7.4 mg/kg bw/day Liver toxicity at 33 mg/kg bw/day	100
Cancer	A threshold approach to hepatocellular adenomas in male mice and thyroid adenomas in male rats used for risk assessment.		

[1] CAF (composite assessment factor) refers to a total of uncertainty and *Pest Control Products Act* factors for dietary assessments; MOE refers to a target MOE for occupational and residential assessments

[2] Since an oral NOAEL was selected, a 10% dermal absorption factor was used for route-to-route extrapolation

Appendix II Dietary Exposure and Risk Estimates for MGK-264

Table 1 Dietary Exposure and Risk Estimates for MGK-264

Population Subgroup	Deterministic, Intermediate							
	Acute Dietary (95th percentile)[1]				Chronic Dietary[2]			
	Food Only		Food + Water		Food Only		Food + Water	
	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ARfD	Exposure (mg/kg/day)	%ADI	Exposure (mg/kg/day)	%ADI
General Population	0.036989	4	0.038317	4	0.008111	12	0.009142	13
All Infants (<1 year old)	0.050830	5	0.054015	5	0.010330	15	0.014179	20
Children 1-2 years old	**0.077896**	**8**	**0.079624**	**8**	**0.024930**	**36**	**0.026347**	**38**
Children 3-5 years old	0.063803	6	0.065270	7	0.020355	29	0.021508	31
Children 6-12 years old	0.045218	5	0.046398	5	0.012852	18	0.013709	20
Youth 13-19 years old	0.028728	3	0.029832	3	0.007247	10	0.007974	11
Adults 20-49 years old	0.026246	3	0.027666	3	0.006590	9	0.007613	11
Adults 50-99 years old	0.021748	2	0.022983	2	0.005746	8	0.006741	10
Females 13-49 years old	0.023555	2	0.025001	3	0.006076	9	0.007082	10

[1]Acute Reference Dose (ARfD) of 1 mg/kg bw applies to the general population and all population subgroups.
[2]Acceptable Daily Intake (ADI) of 0.07 mg/kg bw/day applies to the general population and all population subgroups.

Appendix III Food Residue Chemistry Summary

MGK-264 is primarily registered as an insecticide synergist for natural pyrethrins and other synthetic pyrethroids. As a synergist, MGK-264 acts by inhibiting insect detoxication systems, thereby reducing the oxidative breakdown of the co-formulated insecticides. Formulations containing MGK-264 are registered in a variety of commercial- and domestic-class products for the control of nuisance insects and of food or non-food product contaminating insects in non-food plants, food and non-food handling establishments, warehouses, outdoor premises, housing for veterinary and farm animals, and as direct application on veterinary and non-food animals. MGK-264 is not registered for use on agricultural growing crops, and application on livestock intended for food production is currently not supported by the registrant of the technical grade active ingredient. Therefore, labels of all products containing MGK-264 must include the following statement: "Cover or remove exposed food and food handling surfaces prior to application". All commercial-class products must include the following statement: "Application on livestock intended for food production is prohibited".

Because no agricultural crop uses are registered and application on livestock intended for food production is not supported, related residue chemistry data requirements are not applicable for the current uses of MGK-264. In other words, metabolism studies in livestock and plants are not required. The residue to be regulated on food commodities, resulting from uses in food handling establishments and warehouses is proposed to be expressed as MGK-264 *per se*, provided that the food commodities are removed or covered prior to such uses, except for bagged food in warehouse storage, which need not be removed or covered prior to applications. This residue definition is also used for dietary risk assessment purposes.

Currently, there are no MRLs established for residues of MGK-264 under the *Pest Control Products Act*. Residues of MGK-264 in all commodities are regulated under subsection B.15.002(1) of the *Food and Drugs Regulations*, which requires that residues do not exceed 0.1 ppm (General MRL). No change to this regulatory status is being proposed. A tolerance of 5 ppm is currently established in the United States for residues of MGK-264, including its metabolites and degradates, in or on all food items in food handling establishments where food and food products are held, processed, prepared and/or served, provided that the food is removed or covered prior to such use, except for bagged food in warehouse storage which need not be removed or covered prior to applications.

Residue data from simulated trials in warehouses and food handling establishments and analytical methods were submitted to the PMRA as well as the USEPA data evaluation records of these studies. The studies were deemed acceptable by the PMRA and constituted the basis for the present re-evaluation of MGK-264. MGK-264 residues are determined using a GLC method with electron capture detector. The USEPA noted that this method is a modification of Method I from Pesticide Analytical Methods Vol. II. Modifications were performed to remove interfering materials and to include a bromination step. The American agency concluded that this method is adequate for data collection purposes and, because it is based on Method I from Pesticide Analytical Methods Vol. II, the method was deemed also adequate for enforcement purposes. MGK-264 is not included in the scope of the current CFIA Multiresidue Analytical Method.

Sufficient data were available to adequately assess the dietary exposure and risk from exposure to MGK-264. Due to the extent of supported outdoor uses, EECs were modelled in order to estimate the potential contamination of drinking water sources.

Appendix IV Commercial Mixer/Loader/Applicator Risk Assessment

Table 1 Occupational Mixer/Loader/Applicator Exposure and Risk Assessment (Intermediate-Term)

Application Equipment	Scenario[a]	Application Rate[b]	ATPD[c]	Exposure[d] (ug/kg bw/day)		MOE	
				Dermal	Inhalation	Dermal[e] (T=100)	Inhalation[f] (T=300)
Short Sleeved Shirt, Shorts, No Gloves							
Trigger pump sprayer[g]	Horse & Pony spray	0.432 g a.i./animal	26 animal	254	1.02	394	1860
Wipe on[h]				56.1	0.10	1780	18,200
Trigger pump sprayer[g]	Pets	1.27 g a.i./animal	8 pets	230	0.92	436	2060
Shampoo[g]				560	0.08	179	23400
Dropper bottle[g] (gloves)[m]				33.6	Negligible	2980	N/A
Single Layer, No Gloves							
Aerosol	C&C[n], spot/band[n], Space spray[n], mosquito abatement, pets[n]	15 g a.i./can[i]	4 cans	284	1.23	352	1540
	Metered Release	0.032 g a.i./m^3[j]	680 m^3[j]	103	0.45	968	4230
Automatic, Stationary- ULV aerosol generator, mechanical aerosol generator, fogger, mistblower[l]	Space spray	0.167 g a.i./m^3[j]	680 m^3[j]	0.07	<0.01	1,380,000	837,000
	Mosquito abatement	78.5 g a.i./ha	405 ha	20.3	0.64	4920	3000
Handheld- ULV aerosol generator, mechanical aerosol generator, fogger, mistblower[l]	Space spray, mosquito abatement	No data					
Single Layer, CR Gloves							
Backpack	Outdoors, mosquito abatement	0.091 g a.i./m^2[k]	4047 m^2[k]	25.1	0.29	3990	6650
Man PHW	Outdoors[n], mosquito abatement	0.091 g a.i./m^2[k]	4047 m^2[k]	4.34	0.21	23,000	9130

Application Equipment	Scenario[a]	Application Rate[b]	ATPD[c]	Exposure[d] (ug/kg bw/day)		MOE	
				Dermal	Inhalation	Dermal[e] (T=100)	Inhalation[f] (T=300)
Mech PHG[o]	Outdoors, mosquito abatement	0.091 g a.i./m^2	20,000 m^2	127	3.44	787	553
Single Layer, CR Gloves (MLA), Chem. Resist Hat (A).							
Truck mounted ULV aerosol generator[l]	Mosquito abatement	78.5 g a.i./ha	405 ha	185	4.24	540	448
Single Layer, CR gloves (MLA), Respirator							
Man PHW, ULV aerosol generator, mechanical aerosol generator[g]	C&C[m], spot/band[n]	0.46 g a.i./m^2	1040 m^2	422	3.04	237	625
	Broadcast[n]		3716 m^2	118	8.51	847	2230
	Space spray[n]	0.0954 g a.i./m^3	680 m^3	16.01	1.15	6250	1650

ATPD = Area Treated per Day or amount handled per day; MOE = Margin of Exposure; MLA = Mixer/Loader/Applicator; A = applicator; Mech PHG = Mechanically Pressurized Hand Gun; Man PHW = Manually Pressurized Hand Wand; T = Target MOE; CR = chemical resistant; ULV = ultra low volume; C&C = crack and crevice; N/A = not applicable

[a] The application method or scenario where the application equipment may be used.

[b] Maximum rates were used for each scenario/application equipment.

[c] Area treated or amount handled values.

[d] Exposure = Unit Exposure (µg/kg a.i.) * ATPD * Application Rate / Body Weight (80 kg). Unit exposures from PHED or AHETF.

[e] Dermal MOEs are based on a NOAEL of 100 mg/kg bw/day from a dermal toxicity. Target is 100.

[f] Inhalation MOEs are based on a LOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study. Target is 300.

[g] Unit exposure from the USEPA Residential SOPs (2012) were assumed as commercial applicator unit exposures were not available for this equipment type. PPE is reflective of what a residential applicator is assumed to wear and may be conservative for commercial and professional applicators who may wear pants and long-sleeved shirts.

[h] Paintbrush PHED unit exposure data were used as surrogate, as no data were available. This is considered to be an overestimate of exposure.

[i] Automated, stationary foggers are assumed in the risk assessment (assume exposure from mixing/loading only). No measured exposure data are available for handheld foggers/mistblowers or handheld ULV space spray applications, so their use will be prohibited on the label.

[j] Maximum guarantee (3.33%) from all commercial products for aerosol application (not metered release) and default can size used (453 g).

[k] No 'no glove' scenarios were available in PHED for the handheld equipment.

[l] Airblast application equipment was used as surrogate for truck-mounted ULV sprayer.

[m] Gloves are worn in the spot-on study used as surrogate for the dropper bottle scenario.

[n] Indicated as regularly used by commercial applicators for these scenarios in the Canadian Pest Management Association (CPMA) survey.

[o] Not included for indoor applications, as indicated in the CPMA survey.

[p] PHED wettable powder low pressure handwand unit exposure values were used as surrogate, as no data were available for aerosol generators. Used as surrogate for all indoor pesticide handheld application as it was scenario-specific (indoor crack and crevice application). Other liquid handheld PHED unit exposure values were based on application to chicken houses and greenhouses, which may not be reflective of application exposure for this scenario. It is likely that mixer/loader exposure is overestimated as this is being applied to a liquid formulation; however, it is unknown what portion of the exposure is due to mixing and loading the wettable powder.

Appendix V Non-Occupational Risk Assessment

Summary of Exposure Tables

Use Scenario	Exposure Duration	Exposure Route	Sub-Population Included	Table (specific use) in Appendix V
Mixer/Loader/Applicator				
Commercial	Intermediate-term	Dermal, Inhalation	Adults	Appendix IV, Table 1
Residential	Short-term	Dermal, Inhalation	Adult	Table 1
Postapplication				
Hard and soft surfaces (indoor)-residential, commercial, industrial, institutional, agricultural premises	Short-term	Dermal	Adult, Youth, Children (1<2 yrs)	Table 2, 3
	Intermediate-term			Table 8
	Long-term			Table 9, 10 (bed bug)
	Short-term	Inhalation	Children (3<6 yrs) for agricultural premise-specific scenarios	Table 11 (aerosols) Table 12, 15 (vapours)
	Intermediate-term			Table 13 (metered release)
	Short-term	Incidental Oral	Children (1<2 yrs)	Table 16, 17
	Intermediate-term			Table 22, 23 (metered release)
	Long-term			Table 24, 25 (bed bug)
Gardens and trees (outdoor)	Short-term	Dermal	Adults, Youth, Children (6<11 yrs)	Table 4
	Inhalation risk assessment not required inhalation exposure to vapours is expected to be low based on the low vapour pressure of MGK-264 and dilution of any potential airborne concentration with the large airspace outside.			
	Incidental oral risk assessment not required for children 6<11 yrs			
Turf (outdoor)	Short-term	Dermal	Adults, Youth, Children (1<2 yrs)	Table 5
	Inhalation risk assessment not required inhalation exposure to vapours is expected to be low based on the low vapour pressure of MGK-264 and dilution of any potential airborne concentration with the large airspace outside.			
	Short-term	Incidental Oral	Children (1<2 yrs)	Table 18, 19, 20

Mosquito abatement (outdoor)	Dermal risk assessment for this scenario not required, as this use is addressed by the gardens and trees, and turf scenarios.			
	Short-term	Inhalation	Adults, Youth, Children (1<2 yrs)	Table 14
	Incidental oral risk assessment for this scenario not required, as this use is addressed by the turf scenarios			
Treated pets	Short-term	Dermal	Adults, Youth, Children (1<2 yrs)	Table 6.7
	Inhalation risk assessment not required inhalation exposure to vapours is expected to be low based on the low vapour pressure of MGK-264.			
	Short-term	Incidental Oral	Children (1<2 yrs)	Table 21

Table 1 Residential Mixer/Loader/Applicator Exposure and Risk Assessment (Short-Term)

Application Equipment	Scenario[a]		Application Rate[b]	ATPD[c]	Exposure[d] (mg/kg bw/day)		MOE	
					Dermal	Inhalation	Dermal[e] (T=100)	Inhalation[f] (T=300)
Short sleeved shirt, shorts, no gloves								
Aerosol	Indoors	Broadcast	4.53 g a.i./can[g]	1 can	0.0462	0.0004	22,000	5100
		Band/spot/ Bedbug		0.5 can	0.0231	0.0002	43,000	10,000
		Space spray		0.25 can	0.0115	0.00009	87,000	20,000
	Outdoors	Ornamentals, wasp nests, ants, structural		2 cans	0.0924	0.0007	11,000	2,500
	Indoors	Metered release	Exposure data not available. Considered to be less than that for applying by aerosol and are not of concern.					
Shaker can	Indoors	Broadcast	5.9 g a.i./ container[h]	1 container	0.699	0.0029	1400	650
Trigger-pump sprayer	Indoor	Broadcast	1.56 g a.i./ container[i]	1 container	0.0037	2.5×10^{-6}	270,000	750,000
		Band/spot		0.5 container	0.0018	1.3×10^{-6}	550,000	1,500,000
Trigger pump sprayer, aerosol	Pets		1.27 g a.i./pet	2 pets	0.057	0.0023	17,000	8200
Shampoo					0.14	0.00002	7100	94,000
Dropper bottle					0.0084	Negligible	120,000	N/A
Roll-on	Horses and Ponies							

ATPD = Area Treated Per Day or amount handled per day; MOE = Margin of Exposure; T = target MOE, N/A = Not Applicable

[a] Application scenario for the application method or use area, as specified.
[b] Maximum rates or container sizes were used for each scenario/application equipment.
[c] Area treated or amount handled values. Default values from the USEPA Residential SOPs (2012) were used where available.
[d] Exposure = Unit Exposure (µg/kg a.i.) * ATPD * Application Rate / Body Weight (80 kg). Unit exposure values from the USEPA Residential SOPs (2012).
[e] Dermal MOEs are based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study. Target is 100.
[f] Inhalation MOEs are based on a LOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study. Target is 300.
[g] Maximum guarantee (1%) from all domestic pressurized product for aerosol application (not metered release) and default can size used (453g) from the USEPA Residential SOPs (2012).
[h] Maximum guarantee (1.18%) from the only domestic dust product and net contents of 500 g.
[i] Maximum guarantee (0.3%) from the domestic liquid product not registered for direct application to pets, product density of 1.0 g/mL, and net contents of 475 mL.

Table 2 Short-Term Postapplication Dermal Exposure from Hard and Soft Surfaces

Exposure Scenario		Life Stage	Transferable Residue (µg/cm^2) [a]	Transfer Coefficient (cm^2/hr)[b]	Exposure Time (hr/day)[c]	Dermal Dose (mg/kg bw/day) [d]	MOE [e] (Target = 100)
Fleas, ticks (max rate of 0.488 g a.i./m^2 for liquids and 0.536 g a.i./m^2 for the domestic dust product)							
Broadcast (0.488 g a.i./m^2)	Soft surface	Adults	2.93	6800	8	1.991	500
		Youth		5600	5	1.438	700
		Children		1800	4	1.917	520
	Hard Surface	Adults	3.90	6800	2	0.664	1500
		Youth		5600	1	0.384	2600
		Children		1800	2	1.28	780
Broadcast (0.0091 g a.i./m^2)	Soft surface	Adults	0.546	6800	8	0.371	2700
		Youth		5600	5	0.268	3700
		Children		1800	4	0.357	2800
	Hard Surface	Adults	0.728	6800	2	0.124	8100
		Youth		5600	1	0.072	14000
		Children		1800	2	0.238	4200
Broadcast Dust- (0.536 g a.i./m^2)	Soft surface	Adults	3.22	6800	8	2.187	460
		Youth		5600	5	1.580	630
		Children		1800	4	2.105	480
Band/Spot (0.488 g a.i./m^2)	Soft surface	Adults	1.45	6800	8	0.996	1000
		Youth		5600	5	0.719	1400
		Children		1800	4	0.958	1000
	Hard Surface	Adults	1.95	6800	2	0.332	3000
		Youth		5600	1	0.192	5200
		Children		1800	2	0.639	1600

Exposure Scenario		Life Stage	Transferable Residue (µg/cm^2) [a]	Transfer Coefficient (cm^2/hr)[b]	Exposure Time (hr/day)[c]	Dermal Dose (mg/kg bw/day) [d]	MOE [e] (Target = 100)
Carpet Beetles (max rate of 0.244 g a.i./m^2)							
Broadcast (0.244 g a.i./m^2)	Soft surface	Adults	1.46	6800	8	0.996	1000
		Youth		5600	5	0.719	1400
		Children		1800	4	0.958	1000
	Hard Surface	Adults	1.95	6800	2	0.332	3000
		Youth		5600	1	0.192	5200
		Children		1800	2	0.639	1600
Broadcast (0.091 g a.i./m^2)	Soft surface	Adults	0.546	6800	8	0.371	2700
		Youth		5600	5	0.268	3700
		Children		1800	4	0.357	2800
	Hard surface	Adults	0.728	6800	2	0.124	8100
		Youth		5600	1	0.072	14000
		Children		1800	2	0.238	4200
Bed Bugs (max rate of 0.244 g a.i./m^2)							
Band/Spot (0.244 g a.i./m^2)	Soft surface	Adults	0.732	6800	8	0.498	2000
		Youth		5600	5	0.360	2800
		Children		1800	4	0.479	2100
	Hard surface	Adults	0.976	6800	2	0.166	6000
		Youth		5600	1	0.096	10,000
		Children		1800	2	0.319	3100
Other Insects (max rate of 0.46 g a.i./m^2 for surface sprays and range of rates for space sprays)							
Band/Spot (0.46 g a.i./m^2)	Soft surface	Adults	1.38	6800	8	0.938	1100
		Youth		5600	5	0.678	1500
		Children		1800	4	0.903	1100
	Hard surface	Adults	1.84	6800	2	0.313	3200
		Youth		5600	1	0.181	5500
		Children		1800	2	0.602	1700
Space spray - max rate for dried fruit processing plants (0.167 g a.i./m^3)	Soft surface	Adults	2.44	6800	8	1.66	600
	Hard surface	Adults	3.25	6800	2	0.554	1800
Space spray - max rate for residential areas (0.1 g a.i./m^3)	Soft surface	Adults	1.46	6800	8	0.995	1000
		Youth		5600	5	0.719	1400
		Children		1800	4	0.958	1000
	Hard	Adults	1.95	6800	2	0.332	3000

Exposure Scenario		Life Stage	Transferable Residue (µg/cm^2) [a]	Transfer Coefficient (cm^2/hr)[b]	Exposure Time (hr/day)[c]	Dermal Dose (mg/kg bw/day) [d]	MOE [e] (Target = 100)
	surface	Youth		5600	1	0.192	5200
		Children		1800	2	0.638	1600
Space spray (0.055 g a.i./m^3)	Soft surface	Adults	0.805	6800	8	0.547	1800
		Youth		5600	5	0.395	2500
		Children		1800	4	0.527	1900
	Hard Surface	Adults	1.07	6800	2	0.182	5500
		Youth		5600	1	0.105	9500
		Children		1800	2	0.351	2800
Space spray- min rate (0.003 g a.i./m^3)	Soft surface	Adults	0.0439	6800	8	0.030	34,000
		Youth		5600	5	0.022	46,000
		Children		1800	4	0.029	35,000
	Hard surface	Adults	0.0585	6800	2	0.010	100,000
		Youth		5600	1	0.006	170,000
		Children		1800	2	0.019	52,000

Max = maximum; Min= minimum

[a] Where Transferable Residue (µg/cm^2) = Deposited Residue (µg/cm^2) × Fraction Transferred (%). Deposited residues were calculated based on maximum label application rates and the percent of residues available for exposure (100 and 50%, for broadcast and band/spot/bedbug, respectively). The fraction transferred for soft surfaces was 0.06 and 0.08 for soft surfaces and hard surfaces, respectively.

[b] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs (2012).

[c] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).

[d] Where Dermal Dose (mg/kg bw/day) = (Transferable Residue (µg/cm^2) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/day))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths (11 <16 years), and children (1 <2 years) respectively, as stated in the USEPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.

[e] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to short- term scenarios.

Table 3 Short-Term Postapplication Dermal Exposure from Mattresses

Exposure Scenario	Life Stage	Deposited Residue ($\mu g/cm^2$) [a]	Surface Area/Body Weight Ratio (cm^2/kg)[b]	Dermal Dose (mg/kg bw/day) [c]	MOE [d] (Target = 100)
Bed bugs (max application rate of 0.244 g a.i./m^2)					
Application to mattress	Adults	12.2	280	0.0512	20,000
	Youth				
	Children		640	0.117	8500

[a] Estimated deposited residue, based on band/spot/bed bug deposited residue.
[b] Values were obtained from the USEPA Residential SOPs (2012) for adults and children (1<2 years).
[c] Where Dermal Dose (mg/kg bw/day) = (Deposited Residue ($\mu g/cm^2$) × 0.001 mg/µg × Surface Area/Body Weight Ratio (cm^2/kg) × Fraction of skin in contact with mattress (0.5) × Fraction transferred (0.06) × Protection Factor (0.5). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[d] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to short-term scenarios.

Table 4 Short-Term Postapplication Dermal Exposure from Gardens and Trees[a]

Exposure Scenario	Life Stage	DFR_t (ug/cm^2)[b]	Transfer Coefficient (cm^2/hr)[c]	Exposure Time (hour)[d]	Dermal Dose (mg/kg bw/day)[e]	MOE [f] (Target = 100)
Gardens	Adults	1.04	8400	2.2	0.239	4180
	Youth		6900	1.1	0.138	7250
	Children		4600	1.1	0.164	6110
Trees	Adults		1700	1	0.022	45,500
	Youth		1400	0.5	0.013	78,700
	Children		930	0.5	0.015	66,500

[a] The risk assessment was conducted without chemical-specific DFR since no studies were provided. The peak DFR (day 0) default of 25% of the application rate and 10% dissipation per day was assumed.
[b] DFRt = dislodgeable foliar residue at time (t) where t is the day of the second application. DFR_t = Application Rate (kg a.i./ha) × 0.25+ (application rate × 0.25 × (1-(Dissipated Residue (0.1))^t (day after application (0)) × 1.0E09 ug/kg × 1.0 E-08 ha/cm^2). Based on 2 applications 2 weeks apart.
[c] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs (2012).
[d] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).
[e] Where Dermal Dose (mg/kg bw/day) = (DFR_t ($\mu g/cm^2$) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr)/Body Weight (kg). Body weights of 80, 57 and 32 kg were used for adults, youths, and children (6 <11 years) as stated in USEPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.

[f] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to short-term scenarios.

Table 5 Short-Term Postapplication Dermal Exposure from Lawns and Turf[a]

Exposure Scenario	Life Stage	TTR_t (ug/cm^2)[b]	Transfer Coefficient (cm^2/hr)[c]	Exposure Time (hour)[d]	Dermal Dose (mg/kg bw/day)[e]	MOE [f] (Target = 100)
Ants	Adults	0.30	180,000	1.5	1.01	990
	Youth		148,000	1.3	1.01	990
	Children		49,000	1.5	2.00	500
Perimeter and Flea	Adults	0.11	180,000	1.5	0.377	2600
	Youth		148,000	1.3	0.377	2600
	Children		49,000	1.5	0.747	1300

[a] The risk assessment was conducted without chemical-specific DFR since no studies were provided. The peak TTR (day 0) default of 1% of the application rate and 10% dissipation per day was assumed.
[b] TTRt = turf transferrable residue at time (t) where t is the day of the second application. Where TTR_t = (Application Rate (kg a.i./ha) × 0.01) × (Application Rate × 0.01 × (1-(Dissipated Residue (0.1))^t (day after application (0)) × 1.0E09 ug/kg × 1.0 E-08 ha/cm^2). Based on 2 applications 2 weeks apart.
[c] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs (2012).
[d] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).
[e] Where Dermal Dose (mg/kg bw/day) = (TTR_t (µg/cm^2) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr)/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths, and children (1<2 years) as stated in USEPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[f] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to short-term scenarios.

Table 6 Short-Term Postapplication Dermal Exposure from Treated Pets Using Residential SOP Approach[a]

Exposure Scenario		Life Stage	Surface Area of Pet (cm^2/animal)[b]	Transferable Residue (mg/cm^2)[c]	Transfer Coefficient (cm^2/hr)[d]	Exposure Time (hours/day)[e]	Dermal Dose [f] (mg/kg bw/day)	MOE [g] (Target = 100)
USEPA Residential SOP (2012) Approach								
Dog	Small	Adults	3000	0.008	5200	0.77	0.424	2400
		Youth			4300	0.92	0.588	1700
		Children			1400	1	1.08	930
	Medium	Adults	7000	0.004	5200	0.77	0.182	5500
		Youth			4300	0.92	0.252	4000

Exposure Scenario		Life Stage	Surface Area of Pet (cm^2/animal)[b]	Transferable Residue (mg/cm^2)[c]	Transfer Coefficient (cm^2/hr)[d]	Exposure Time (hours/day)[e]	Dermal Dose[f] (mg/kg bw/day)	MOE[g] (Target = 100)
Cat	Large	Children	11000	0.002	1400	1	0.462	2200
		Adults			5200	0.77	0.116	8700
		Youth			4300	0.92	0.160	6200
		Children			1400	1	0.294	3400
	Small	Adults	1500	0.017	5200	0.77	0.848	1200
		Youth			4300	0.92	1.18	850
		Children			1400	1	2.16	460
	Medium	Adults	2500	0.010	5200	0.77	0.509	2000
		Youth			4300	0.92	0.705	1400
		Children			1400	1	1.29	770
	Large	Adults	4000	0.006	5200	0.77	0.318	3100
		Youth			4300	0.92	0.441	2300
		Children			1400	1	0.808	1200

[a] Using the equations and inputs, as outlined in the USEPA Residential SOPs (2012)
[b] Default surface areas for cats and dogs as statement in the USEPA Residential SOPs (2012).
[c] Where Transferable Residue (mg/cm^2) = Application Rate (mg a.i./pet) × Fraction of application rate transferred (0.02)/ Surface Area of pet cm^2/pet.
[d] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs (2012).
[e] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).
[f] Where Dermal Dose (mg/kg bw/day) = (Transferable Residue (mg/cm^2) × Transfer Coefficient (cm^2/hr) × Exposure Time (hour/day)/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths, and children (1 <2 yrs) as stated in USEPA Residential SOPs (2012). Dermal absorption not required because the dermal NOAEL is based on a dermal toxicity study.
[g] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to short-term scenarios.

Table 7 Short-Term Postapplication Dermal Exposure from Treated Pets Using Chemical-Specific Data[a]

Exposure Scenario		Lifestage	Application Rate[b]	Unit Exposure[c] (mg/kg a.i./pet)	Dermal Dose[d] (mg/kg bw/day)	MOE[e] (Target = 100)
Dog	4 hours postapplication	Adults	1.27 g a.i./pet	591	0.0094	107,000
		Youth		484	0.0108	92,600
		Children		160	0.0184	64,300
	14 days postapplication	Adults		35.9	0.0006	1,750,000
		Youth		29.4	0.0007	1,520,000
		Children		9.69	0.0011	893,000

[a] Postapplication unit exposures from the chemical-specific study where adults contact dogs following application of a shampoo that contains MGK-264 (Selim, 2005) were used to

estimate dermal exposure. Unit exposure was based on residues found in hand/forearm wipes and t-shirts.
[b] Maximum application rate for pets.
[c] Adult unit exposures from the chemical-specific study were scaled for the surface area of youth and children (1<2 years) using defaults from the USEPA Residential SOPs (2012).
[d] Dermal dose (mg/kg/bw/day) = application rate (g a.i./pet) × 1kg/1000 g × unit exposure (mg/kg a.i.)
[e] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to short-term scenarios.

Table 8 Intermediate-Term Postapplication Dermal Exposure from Hard and Soft Surfaces

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$) [a]	Transfer Coefficient (cm^2/hr) [b]	Exposure Time (hr/day) [c]	Dermal Dose (mg/kg bw/day) [d]	MOE [e] (Target = 100)
Other Insects							
Space spray - metered release (0.91 g a.i./28 m^3)	Soft surface	Adults	0.475	6800	8	0.323	310
		Youth		5600	5	0.234	430
		Children		1800	4	0.311	320
	Hard Surface	Adults	0.634	6800	2	0.108	930
		Youth		5600	1	0.062	1600
		Children		1800	2	0.207	480

[a] Where Transferable Residue ($\mu g/cm^2$) = Residue ($\mu g/cm^2$) × Fraction Transferred (%). Deposited residues were calculated based on the default residues provided in the USEPA Residential SOPs (2012) for all scenarios.
[b] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs (2012).
[c] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).
[d] Where Dermal Dose (mg/kg bw/day) = (Transferable Residue ($\mu g/cm^2$) × 0.001 mg/µg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/day))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths, and children (1 <2 years) respectively, as stated in the USEPA Residential SOPs (2012).
[e] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 100 mg/kg bw/day from a dermal toxicity study and a target MOE of 100 applicable to intermediate-term scenarios.

Table 9 Long-term Postapplication Dermal Exposure from Hard and Soft Surfaces

Exposure Scenario		Life Stage	Transferable Residue ($\mu g/cm^2$) [a]	Transfer Coefficient (cm^2/hr)[b]	Exposure Time (hr/day)[c]	Dermal Dose (mg/kg bw/day) [d]	MOE [e] (Target = 100)
Bed Bugs (max rate of 0.244 g a.i.//m^3)							
Bed bug – commercial application (0.244 g a.i./m^2)	Soft surface	Adults	0.122	4,700	8	0.006	1300
		Youth		3,900	5	0.004	1800
		Children		1,300	4	0.006	1300
	Hard Surface	Adults	0.183	4,700	2	0.002	3400
		Youth		3,900	1	0.001	5900
		Children		1,300	2	0.004	1700

[a] Where Transferable Residue ($\mu g/cm^2$) = Residue ($\mu g/cm^2$) × Fraction Transferred (%). Deposited residues were calculated based on the default residues provided in the USEPA Residential SOPs (2012) for all scenarios. The fraction transferred is based on the 50th percentile values for long-term risk assessments (2% for soft surfaces and 3% for hard surfaces).
[b] Transfer Coefficient (cm^2/hr) default values obtained from the USEPA Residential SOPs (2012) and are based on the 50th percentile values for long-term risk assessments.
[c] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).
[d] Where Dermal Dose (mg/kg bw/day) = (Transferable Residue ($\mu g/cm^2$) × 0.001 mg/μg × Transfer Coefficient (cm^2/hr) × Exposure Time (hr/day) × DA (10%))/Body Weight (kg). Body weights of 80, 57 and 11 kg were used for adults, youths, and children (1 <2 years) respectively, as stated in the USEPA Residential SOPs (2012).
[e] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 7.4 mg/kg bw/day from an oral toxicity study and a target MOE of 100 applicable to long-term dermal scenarios.

Table 10 Long-Term Postapplication Dermal Exposure from Mattresses

Exposure Scenario	Life Stage	Deposited Residue ($\mu g/cm^2$) [a]	Surface Area/Body Weight Ratio (cm^2/kg)[b]	Dermal Dose (mg/kg bw/day) [c]	MOE [d] (Target = 100)
Bed bugs (max application rate of 0.244 ga.i./m^2)					
Application to mattress	Adults	12.2	280	0.0017	4300
	Youth				
	Children		640	0.0039	1900

[a] Default deposited residue value was obtained from the USEPA Residential SOPs (2012) since an application rate was not provided for products applied to mattresses.
[b] Values were obtained from the USEPA Residential SOPs (2012) based on body weights of 80 kg for adults, 57 kg for youth, and 11 kg for children (1<2 years).
[c] Where Dermal Dose (mg/kg bw/day) = (Deposited Residue ($\mu g/cm^2$) × 0.001 mg/μg × Surface Area/Body Weight Ratio (cm^2/kg) × Fraction of skin in contact with mattress (0.5) × Fraction transferred (0.02) × Protection Factor (0.5) × DA (10%).
[d] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 7.1 mg/kg bw/day from an oral toxicity study and a target MOE of 100 applicable to long-term dermal scenarios.

Table 11 Short -Term Postapplication Inhalation Exposure from Aerosols

Exposure Scenario	Life Stage	Initial Concentration, C_o (mg/m^3)[a]	Inhalation Dose (mg/kg bw/day)[b]	MOE [c] (Target = 300)
Indoor Residential Environments				
Space spray (max rate-0.1 g a.i./m^3)[d]	Adults	100	1.05	2
	Youth		1.46	1
	Children (1<2 years old)		3.96	40.5
Space spray (min rate- 0.003g a.i./m^3)[d]	Adults	3.00	0.0316	60
	Youth		0.0437	43
	Children (1<2 years old)		0.119	16
Space spray (domestic aerosol product)[e]	Adults	37.4	0.394	5
	Youth		0.544	4
	Children (1<2 years old)		1.48	1
Space spray (2 hours after application)[f]	Adults	0.026[f]	0.000416[g]	4600
	Youth		0.000575[g]	3300
	Children (1<2 years old)		0.00156[g]	1200
Indoor Dried Fruit Processing Plants				
Space spray (max rate-0.167 g a.i./m^3)[d]	Adults	167	1.76	1
Space spray (min rate- 0.13 g a.i./m^3)[d]	Adults	130	1.37	1
Indoor Agricultural Premises				
Space spray (max rate-0.0954 g a.i./m^3)[d]	Adults	95.4	0.191	10
	Youth		0.264	7
	Children (3<6 years old)		0.715	3
Space spray (min rate- 0.016 g a.i./m^3)[d]	Adults	16.0	0.0320	59
	Youth		0.0442	43
	Children (3<6 years old)		0.0884	21

Shaded cells indicate where MOEs are less than the target MOE.

[a] Initial Concentration (mg/m^3) = Application Rate (kg a.i./m^3) × 1.00E06 mg/kg.

[b] Inhalation Dose (mg/kg bw/day) = $\frac{C_o \times IR}{ACH \times BW}[1-e^{(-ACH \times ET)}]$

Where IR = Inhalation Rate (m^3/hour) 0.64, 0.63, 0.42 and 0.33 m^3/hr for adult, youth, children (3<6 years old) and children (1<2 years old) respectively, ACH = Air Exchange per hour (0.45 hr^{-1} for residential areas, 4/hr for agricultural premises), ET = Exposure Time (2 hr), BW = Body Weight (80 kg for adults, 57 kg for youth, 19 kg for children (3<6 years old) and 11 kg for children (1<2 years old). Default values were obtained from the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; MOE = NOAEL/Exposure, based on a LOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study and a target MOE of 300 applicable to short-intermediate-term scenarios.

[d] Minimum and maximum application rate as per the master label, or Canadian labels, where information on application rate are available.

[e] Calculated for domestic applicators, assuming that 0.25 of the can is used per room (33m^3), the max guarantee in domestic space spray products and the default density of the product is 1 g/mL.

[f] Air concentration value from chemical-specific study (Selim and Kreiger, 2004). Residues were below the LOQ after 2 hours, so the LOQ of 0.026 mg/m^3 was used in the assessment.

[g] Inhalation dose was calculated = AC × IR × ET/BW. Where inhalation rates and body weights were the same as for other scenarios (footnote 'b' above).

Table 12 Short -Term Postapplication Inhalation Exposure from Indoor Vapours

Exposure Scenario	Life Stage	Mass of a.i. (mg) [a]	Exposure Time (hour) [b]	Inhalation Dose (mg/kg bw/day) [c]	MOE [d] (Target = 300)
Indoor Residential Environments- Commercial Application					
Fleas, ticks, carpet beetles (0.091 g a.i./m^2): Handheld broadcast	Adults	1219	16	0.00906	2100
	Youth		15	0.00116	1600
	Children (1<2 years)		18	0.00389	490
Fleas, ticks (max rate- 0.488 g a.i./m^2): Aerosol broadcast	Adults	976	16	0.000725	2600
	Youth		15	0.000929	2000
	Children (1<2 years)		18	0.00311	610
Fleas, ticks (max rate- 0.488 g a.i./m^2): Aerosol spot/band	Adults	102	16	0.000076	25,000
	Youth		15	0.000098	19,000
	Children (1<2 years)		18	0.000327	5800
Carpet beetles (0.244 g a.i./m^2): Aerosol broadcast	Adults	488	16	0.000362	5200
	Youth		15	0.000464	4100
	Children (1<2 years)		18	0.00156	1200

Exposure Scenario	Life Stage	Mass of a.i. (mg) [a]	Exposure Time (hour) [b]	Inhalation Dose (mg/kg bw/day) [c]	MOE [d] (Target = 300)
Bed bugs (max rate-0.244 g a.i./m^3): Aerosol spot/band	Adults	488	16	0.000362	5200
	Youth		15	0.000464	4100
	Children (1<2 years)		18	0.00156	1200
Other insects (max rate- 0.46 g a.i./m^3): Handheld spot/band	Adults	2070	16	0.00154	1200
	Youth		15	0.00197	960
	Children (1<2 years)		18	0.00660	290 [e]
Other insects (max rate- 0.244 g a.i./m^3): Aerosol spot/band	Adults	488	16	0.000362	5200
	Youth		15	0.000464	4100
	Children (1<2 years)		18	0.00156	1200
Other insects space spray (max rate, dried fruit processing plants- 0.167 g a.i./m^3)	Adults	5511	16	0.00409	460
Other insects space spray (max rate, residential areas-0.1 g a.i./m^3)	Adults	3300	16	0.0025	780
	Youth		15	0.0031	600
	Children		18	0.0012	180
Other insects space spray (0.055 g a.i./m^3)	Adults	1815	16	0.00135	1400
	Youth		15	0.00173	1100
	Children (1<2 years)		18	0.00579	330
Other insects space spray (min rate, 0.003 g a.i./m^3)	Adults	9900	16	0.0000734	26000
	Youth		15	0.0000943	2000
	Children (1<2 years)		18	0.000316	6000
Indoor Residential Environments- Domestic Application					
Fleas - dust broadcast (max guarantee-1.18%)	Adults	5900	16	0.0044	430
	Youth		15	0.0056	340
	Children (1<2 years)		18	0.019	100

Exposure Scenario	Life Stage	Mass of a.i. (mg) [a]	Exposure Time (hour) [b]	Inhalation Dose (mg/kg bw/day) [c]	MOE [d] (Target = 300)
Fleas- Aerosol broadcast (guarantee-1%)	Adults	4530	16	0.00337	560
	Youth		15	0.00431	440
	Children (1<2 years)		18	0.0144	130
Fleas, ticks- Aerosol broadcast (guarantee-0.4%)	Adults	906	16	0.0067	2800
	Youth		15	0.0086	2200
	Children		18	0.0029	660
Fleas, ticks- Trigger pump spray broadcast (max guarantee-0.33%)	Adults	1560	16	0.00116	1600
	Youth		15	0.00149	1300
	Children (1<2 years)		18	0.00500	380
Bed bugs, other insects- aerosol spot/band (max guarantee-1%)	Adults	2265	16	0.00168	1100
	Youth		15	0.00216	880
	Children (1<2 years)		18	0.00722	260 [e]
Other insects - trigger pump spray spot/band (guarantee-0.33%)	Adults	780	16	0.000579	3300
	Youth		15	0.000742	2600
	Children (1<2 years)		18	0.00249	760
Other insects - aerosol space spray (max guarantee-1%)	Adults	1133	16	0.00084	2300
	Youth		15	0.0011	1800
	Children (1<2 years)		18	0.0036	530
Indoor Agricultural Premises					
Other insects space spray (0.0954 g a.i./m^3)	Adults	31,482	4	0.00364	520
	Youth		4	0.00503	380
	Children (3<6 years)		2	0.00320	590
Indoor Residential Environments- Commercial Application- Sensitivity Analysis for Scenarios where MOEs<Target MOE [f]					
Other insects space spray (max rate, residential areas-0.1 g a.i./m^3)	Children (1<2 years)	3300	18	0.0012	180
			12 (modified)	0.0065	300
	Children (3<6 years)		16	0.0068	280

Shaded cells indicate where the MOE is much lower than the target MOE.

[a] For commercial products mass of a.i. = M_{Label} = Application Rate (g a.i./m^2) × area treated in a room (13.8 m^2 for broadcast, 4.5 m^2 for band/spot for handheld and 6 m^2 for aerosol) × 1.00E+03. For domestic products Mass of a.i. = M_{Label} = Application Rate (kg a.i./can) × Amount Handled (1 can for broadcast, 0.5 can for band/spot, 0.25 cans for space spray) × 1.00E+06. Application rate calculated based on the default container size (453 g) from the Res SOPs (2012) for aerosol and max container size for solutions and % a.i. guarantee.

[b] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).

[c] Where inhalation exposure (mg/kg bw/day) = $\frac{IR \times M}{ACH \times V} \times 1\left[-\left[\frac{(ACH \times e^{-k \times ET}) - (k \times e^{-ACH \times ET})}{ACH - k}\right]\right] \times \frac{1}{BW}$

The equation assumes 100% absorption through inhalation, air exchanges (ACH) = 0.45 hr^{-1}, volume of a room (V) = 33 m^3, decay rate (k) = 9.5E-06 hr^{-1}, M = mass of a.i., ET = exposure time. Inhalation rates (IR) of 0.64, 0.63, 0.42, and 0.33 m^3/hr and body weights (BW) of 80, 57, 19, and 11 kg were used for adults, youth, children (3<6 years old), and children (1<2 years old) respectively, as stated in the USEPA Residential SOPs (2012).

[d] MOE = margin of exposure; MOE = NOAEL/Exposure, based on a NOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study and a target MOE of 300 applicable to short-intermediate-term scenarios.

[e] MOEs are below the target MOE, but considered to be acceptable given the conservatisms in the risk assessment.

[f] The sensitivity analysis was conducted to help determine what registered residential scenarios would give risks of concern. For children (1<2 years) the exposure time at which the target MOE would be met was determined (as indicated by 'modified'). An inhalation risk assessment for children (3<6 years) were also included. The results of this analysis will be used to inform the label mitigation for this use.

Table 13 Intermediate -Term Postapplication Inhalation Exposure for Metered Release Products

Exposure Scenario	Life Stage	Air Concentration (µg/m^3)[a]	Exposure Time (hour)[b]	Inhalation Dose (mg/kg bw/day)[c]	MOE [d] (Target = 300)
Indoor Residential Environments	Adults	0.045 (1.8 m away from device)	16	0.00577	330
	Youth		15	0.00747	250
	Children (1<2 years old)		18	0.0243	78
	Adults	0.038 (avg of both distances)	16	0.00490	390
	Youth		15	0.00635	300
	Children (1<2 years old)		18	0.0201	92
Agricultural Premises	Adults	0.045 (1.8 m away from device)	4	0.00144	1300
	Youth		4	0.00199	950
	Children (3<6 years old)		2	0.00199	950
	Adults	0.038 (avg of both distances)	4	0.00123	1600
	Youth		4	0.00169	1100
	Children (1<2 years old)		2	0.00169	1100

Sensitivity Analysis for Scenarios where MOEs<Target MOE[e]					
Indoor Residential Environments	Youth	0.045 (1.8 m away from device)	13 (modified)	0.0065	290
	Children (1<2 years old)		5 (modified)	0.0067	280
	Children (3<6 years old)		16	0.0159	120
			7 (modified)	0.0070	270
	Children (1<2 years old)	0.038 (avg of both distances)	6 (modified)	0.0069	280
	Children (3<6 years old)		16	0.0135	140
			8 (modified)	0.0068	280

Shaded cells indicate where MOEs are less than the target MOE.

[a] Average air concentration from chemical-specific study (peak to end of study) after metered release spray (Selim, 2008) at 1.8 m away and for both 1.8 and 3.0 m away from the device.

[b] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012) for vapours for indoor residential environments and barn misting systems for agricultural premises.

[c] Inhalation dose was calculated = AC × IR × ET/BW. Where IR = Inhalation Rate (m^3/hour) 0.64, 0.63, 0.42 and 0.33 m^3/hr for adult, youth, children (3<6 years old) and children (1<2 years old) respectively, ET = Exposure Time (2 hr), BW = Body Weight (80 kg for adults, 57 kg for youth, 19 kg for children (3<6 years old) and 11 kg for children (1<2 years old). Default values were obtained from the USEPA Residential SOPs (2012).

[d] MOE = margin of exposure; MOE = NOAEL/exposure, based on a LOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study and a target MOE of 300 applicable to short-intermediate-term scenarios.

[e] The sensitivity analysis was conducted to help determine what registered residential scenarios would give risks of concern. For children (1<2 years) the exposure time at which the target MOE would be met was determined (as indicated by 'modified'). An inhalation risk assessment for children (3<6 years) were also included. The results of this analysis will be used to inform the label mitigation for this use.

Table 14 Short-Term Postapplication Inhalation Exposure from Mosquito Abatement

Exposure Scenario	Life Stage	Air Concentration [a]	Fraction Available [b]	Exposure Time (hour)[c]	Inhalation Dose (mg/kg bw/day)[c]	MOE [e] (Target = 300)
Mosquito abatement (0.00785 g a.i./m^2)	Adults	15.7 mg/m^3	1%	1.5	0.00188	1008
	Youth			1.3	0.0226	842
	Children			1.5	0.00707	269[f]

[a] Air concentration was determined by assuming the application rate (0.00785 g a.i./m^2) is available in a 0.5 m high area.

[b] Fraction of chemical available in outdoor air for exposure used to adjust amount of chemical released for "infinite dilution" attributable to being outdoors.

[c] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012) for lawns and turf.

[d] Where inhalation exposure (mg/kg bw/day) = air concentration × fraction available × inhalation rate × exposure time/ body weight. Inhalation rates (IR) of 0.64, 0.63 and 0.33 m^3/hr and body weights (BW) of 80, 57 and 11 kg were used for adults, youth and children (1<2 years old) respectively, as stated in the USEPA Residential SOPs (2012).

[e] MOE = margin of exposure; MOE = NOAEL/Exposure, based on a NOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study and a target MOE of 300 applicable to long-term scenarios.
[f] Considered to be close to the target MOE given then conservatisms in the risk assessment.

Table 15 Long-Term Postapplication Inhalation Exposure from Indoor Surface Directed Sprays

Exposure Scenario	Life Stage	Mass of a.i. (mg) [a]	Exposure Time (hour) [b]	Inhalation Dose (mg/kg bw/day) [c]	MOE [d] (Target = 1000)
Bed bugs (max rate-0.244 g a.i./m^2): Aerosol spot/band	Adults	488	16	0.000363	5200
	Youth		15	0.00464	4100
	Children		18	0.00156	1200

Shaded cells indicate where the MOE is much lower than the target MOE.
[a] Mass of a.i. = M_{label} = Application Rate (g a.i./m2) × area treated in a room (highest amount per room from CPMA survey for aerosol- 2 m^2) × 1.00E+03.
[b] Exposure Time (hr/day) default values obtained from the USEPA Residential SOPs (2012).
[c] Where inhalation exposure (mg/kg bw/day) = $\frac{IR \times M}{ACH \times V} \times 1\left[-\left[\frac{(ACH \times e^{-k \times ET}) - (k \times e^{-ACH \times ET})}{ACH - k}\right]\right] \times \frac{1}{BW}$,

The equation assumes 100% absorption through inhalation, air exchanges (ACH) = 0.45 hr^{-1}, volume of a room (V) = 33 m^3, decay rate (k) = 9.5E-06 hr^{-1}, M = mass of a.i., ET = exposure time. Inhalation rates (IR) of 0.64, 0.63 and 0.33 m^3/hr and body weights (BW) of 80, 57 and 11 kg were used for adults, youth and children (1<2 years old) respectively, as stated in the USEPA Residential SOPs (2012).
[d] MOE = margin of exposure; MOE = NOAEL/exposure, based on a NOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study and a target MOE of 1000 applicable to long-term scenarios.

Table 16 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Hand Residue Loading (mg/interval-cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Fleas/Ticks (max rate of 0.488 g a.i./m^2 for liquids and 0.536 g a.i./m^2 for the domestic dust product)				
Broadcast (max rate- 0.488 g a.i./m^2)	Soft surface	0.00066	0.0180	1800
	Hard Surface	0.00088	0.0120	2800
Broadcast (0.091 g a.i./m^2)	Soft surface	0.00012	0.00335	9800
	Hard Surface	0.00016	0.00223	15,000
Broadcast dust - (0.536 g a.i./m^2)	Soft surface	0.00072	0.0197	1700
Band/Spot (max rate- 0.488 g a.i./m^2)	Soft surface	0.00033	0.00899	3700
	Hard Surface	0.00044	0.00600	5500

Carpet beetle (max rate of 0.244 g a.i./m^2)				
Broadcast (max rate- 0.244 g a.i./m^2)	Soft surface	0.00033	0.00890	3700
	Hard Surface	0.00033	0.00449	7300
Broadcast (0.091 g a.i./m^2)	Soft surface	0.00012	0.00335	9800
	Hard Surface	0.00016	0.00223	15,000
Bed bugs (max rate of 0.244 g a.i./m^2)				
Band/Spot (max rate-0.244 g a.i./m^2)	Soft surface	0.00016	0.00449	7300
	Hard Surface	0.00022	0.00300	11,000
Other insects (max rate of 0.46 g a.i./m^2 for surface sprays and range of rates for space sprays)				
Band/Spot (max rate-0.46 g a.i./m^2)	Soft surface	0.00031	0.00847	3900
	Hard Surface	0.00041	0.00565	5800
Space Spray (max residential rate-0.1 g a.i./m^3)	Soft surface	0.00033	0.00898	3700
	Hard Surface	0.00044	0.00599	5500
Space Spray (0.055 g a.i./m^3)	Soft surface	0.00018	0.00494	6700
	Hard Surface	0.00024	0.00329	10,000
Space Spray (0.003 g a.i./m^3)	Soft surface	0.00001	0.00027	120,000
	Hard Surface	0.00001	0.00018	180,000

[a] Based the dermal postapplication exposure from indoor applications without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.15). Based on the overall maximum application rates, as well as the maximum application rate that have acceptable MOEs for all routes of exposure.

[b] Where Oral Dose (mg/kg bw/day) = [Hand Residue (mg/hr) × (Fraction of hand mouthed/event (0.13) × Exposure Time (hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (20)/Replenishment Intervals (1/hr)}}$)]/ Body Weight (11 kg). Exposure times for soft surfaces and hard surfaces were 4, and 2 hrs, respectively, as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL of 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 17 Short-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario (max rates for all pests)		Object Residue (ug/cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Broadcast (0.488 g a.i./m^2)	Soft surface	2.928	0.038	860
	Hard surface	3.904	0.026	1300
Broadcast (domestic dust)	Soft surface	3.216	0.042	790
Band/Spot/Bedbug (0.244 g a.i./m^2)	Soft surface	1.464	0.019	1700
	Hard surface	1.952	0.013	2600

Space spray (0.1 g a.i./m^3)	Soft surface	1.46	0.019	1700
	Hard surface	1.95	0.013	2600
Space spray (0.055 g a.i./m^3)	Soft surface	0.805	0.011	3100
	Hard surface	1.073	0.007	4700

[a] Where Object Residue = Deposited Residue (ug/cm^2) × Fraction of residue transferred (6% for soft surfaces and 8% for hard surfaces). Deposited residue based on overall maximum application rates.

[b] Where Oral Dose (mg/kg bw/day) = [Object Residue (ug/cm^2) × 0.001 mg/ug × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for soft surfaces and hard surfaces were 4 and 2 hrs, respectively as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 18 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Lawns and Turf

Exposure Scenario	Hand Residue (mg/interval-cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Ants	0.00073	0.0068	4800
Perimeter and flea	0.00027	0.0026	13,000

[a] Based the dermal postapplication exposure from indoor applications without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.06).

[b] Where Oral Dose (mg/kg bw/day) = [Hand Residue (mg/cm^2) × Fraction of hand mouthed/event (0.13) × Exposure Time (hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for turf is 1.5 hours, as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 19 Short-Term Postapplication Object-to-Mouth Exposure to Children from Lawns and Turf

Exposure Scenario	Object Residue (ug/cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Ants	0.300	0.00125	26,000
Perimeter and flea	0.112	0.00047	71,000

[a] Where Object Residue = Turf Transferrable Residue (ug/cm^2) Deposited residue based on overall maximum application rates- 2 applications, 14 days apart.

[b] Where Oral Dose (mg/kg bw/day) = [Object Residue (ug/cm^2) × 0.001 mg/ug × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (8.8)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for turf is 1.5 hours, as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on an oral NOAEL 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 20 Short-Term Postapplication Incidental Soil Ingestion Exposure for Children for Lawns and Turf

Exposure Scenario	Application Rate	Ingestion Rate [a]	Soil volume to weight conversion factor [a]	Oral Dose [b] (mg/kg bw/day)	MOE [c] (Target = 100)
Ants	0.244 g a.i./m^2	50 mg/day	0.67 cm^3/g soil	0.000074	440,000
Perimeter and Flea	0.091 g a.i./m^2			0.000028	1,200,000

[a] Default value from the USEPA Residential SOPs (2016)

[b] Where Oral Dose (mg/kg bw/day) = [Application rate (kg a.i./m^2) × fraction available in the top cm of soil (1) × $1x10^9$ ug/kg × m^2/10,000 cm^2 × soil volume to weight conversion factor × soil ingestion rate × g/$1x10^6$ µg]/ Body Weight (11 kg).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on an oral NOAEL 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 21 Short-Term Postapplication Hand-to-Mouth Exposure to Children from Treated Pets

Exposure Scenario	Animal Size (kg)	Hand Residue Loading (mg/interval-cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Dog	Small	0.0004	0.0027	12,000
	Medium	0.0002	0.0012	29,000
	Large	0.0001	0.0007	45,000
Cat	Small	0.0008	0.0054	6100
	Medium	0.0005	0.0032	10,000
	Large	0.0003	0.0020	16,000

[a] Based the postapplication dermal exposure from spot- on applications without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.04).

[b] Where Oral Dose (mg/kg bw/day) = [Hand Residue (mg/cm^2) × Fraction of hand mouthed/event (0.13) × Exposure Time (hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (20)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure time of 1 hour as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL 100 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 22 Intermediate-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Hand Residue Loading (mg/interval-cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Other Insects (max rate of 0.46 g a.i./m^2 for surface sprays and range of rates for space sprays)				
Space Spray-Metered Release (0.91 g a.i./28 m^3)	Soft surface	0.0011	0.00291	11,000
	Hard Surface	0.00014	0.00194	17,000

[a] Based the dermal postapplication exposure from indoor applications without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.15). Based on the overall maximum application rates, as well as the maximum application rate that have acceptable MOEs for all routes of exposure.

[b] Where Oral Dose (mg/kg bw/day) = [Hand Residue (mg/cm^2) × Fraction of hand mouthed/event (0.13) × Exposure Time (hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (20)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for soft surfaces and hard surfaces were 4, and 2 hrs, respectively, as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on an NOAEL 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 23 Intermediate-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario (max rates for all pests)		Object Residue (ug/cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Space Spray-Metered Release (0.91 g a.i./28 m^3)	Soft surface	0.475	0.006	5300
	Hard Surface	0.634	0.004	8000

[a] Where Object Residue = Deposited Residue (ug/cm^2) × Fraction of residue transferred (6% for soft surfaces and 8% for hard surfaces). Deposited residue based on overall maximum application rates.

[b] Where Oral Dose (mg/kg bw/day) = [Object Residue (ug/cm^2) × 0.001 mg/ug × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for soft surfaces and hard surfaces were 4 and 2 hrs, respectively as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL 33 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 24 Long-Term Postapplication Hand-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Hand Residue Loading (mg/interval-cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Bed Bugs (max rate- 0.244 g a.i./m^2)				
Spot/band	Soft surface	0.00002	0.00047	16,000
	Hard surface	0.00003	0.00035	21,000

[a] Based the dermal postapplication exposure from indoor applications without the body weight/(dermal exposure time (hour) × replenishment intervals (intervals/hr)) × fraction of a.i. on hands compared to body (0.15).

[b] Where Oral Dose (mg/kg bw/day) = [Hand Residue (mg/cm^2) × Fraction of hand mouthed/event (0.12) × Exposure Time (hr) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (14)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for soft surfaces and hard surfaces were 4, and 2 hrs, respectively, as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL 7.4 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Table 25 Long-Term Postapplication Object-to-Mouth Exposure to Children from Indoor Environments

Exposure Scenario		Object Residue (ug/cm^2) [a]	Oral Dose (mg/kg bw/day) [b]	MOE [c] (Target = 100)
Bed Bugs (max rate- 0.244 g a.i./m^2)				
Spot/band	Soft surface	0.122	0.002	4900
	Hard surface	0.183	0.001	6500

[a] Where Object Residue = Deposited Residue (ug/cm^2) × Fraction of residue transferred (2% for soft surfaces and 3% for hard surfaces). Deposited residue based on default residues provided in the USEPA Residential SOPs (2012).

[b] Where Oral Dose (mg/kg bw/day) = [Object Residue (ug/cm^2) × 0.001 mg/ug × Surface Area of object mouthed (10 cm^2/event) × (Exposure Time (hr) × Replenishment Intervals (4/hr)) × (1 – (1 – Saliva Extraction Factor (0.48)) $^{\text{Number events per hour (12)/Replenishment Intervals (4/hr)}}$)]/ Body Weight (11 kg). Exposure times for soft surfaces and hard surfaces were 4 and 2 hrs, respectively as stated in the USEPA Residential SOPs (2012).

[c] MOE = margin of exposure; Oral MOE = NOAEL/Oral exposure, based on a NOAEL 7.4 mg/kg bw/day from an oral toxicity study and a target MOE of 100.

Appendix VI Aggregate Risk Assessment

Table 1 Combined Short-Term Residential Applicator and Postapplication Exposure for Adults

Form	M/L/A Scenario	Homeowner M/L/A Exposure[a] (mg/kg bw/day)		Postapplication Scenario		Postapplication Exposure[b] (mg/kg bw/day)		Combined MOE[c] (MLA + PA)	
		Dermal	Inhalation			Dermal	Inhalation	Dermal (T = 100)	Inhalation (T = 300)
Indoor Residential Areas									
Aerosol	Aerosol surface spray (B)[d]	0.0602	0.0005	0.488 g a.i./m^2 (B)[d]	Soft surface[e]	1.99[h]	0.00135	488	390
					Hard surface[e]	0.664[h]		1380	
	Aerosol surface spray (SB)[d]	0.0301	0.002	0.46 g a.i./m^2 (SB)	Soft surface	0.938[i]	0.00168	1030	986
					Hard surface	0.323[i]		2920	
Ready-to-Use	Trigger pump sprayer (B)[d]	0.0014	0.000001	0.488 g a.i./m^2 (B)[d]	Soft surface	1.99	0.00116	502	1640
					Hard surface	0.664		1500	
All	Domestic Space Spray postapplication scenarios did not reach the target MOEs for all sub-populations.								
Dust	Domestic dust postapplication inhalation scenarios did not reach the target MOE for all sub-populations								
Lawns and Turf									
Aerosol	Aerosol can (ants)	0.230	0.0019	Ants		1.01	N/A[f]	806	1020
	Aerosol can (perimeter)	0.0918	0.0007	Perimeter/Fleas		0.377		2130	2560
Ready-to-Use	Trigger pump sprayer (perimeter)	0.0028	0.000002					2630	970,000
Gardens and Trees									
Aerosol	Aerosol Can	0.0918	0.0007	Gardens		0.239	N/A[f]	3020	2560
				Trees		0.0220		8790	
Treated Pets									
Ready-to-Use	Trigger pump sprayer, aerosol	0.0574	0.0002	Small cat[g]		0.848	N/A[f]	1110	8220
	Shampoo	0.140	0.00002					1010	93,500
	Spot-on	0.0084	Negligible					1170	N/A

Form = formulation; M/L/A = mixer/loader/applicator; MOE = margin of exposure; T = target MOE; N/A= not applicable; (B) = broadcast application; (SB) = spot/band

[a] Exposure from Appendix IV, Table 1.

[b] Dermal exposure from Appendix V, Tables 2, 4-6. Inhalation exposure from Appendix V, Table 12 (vapours).

[c] MOE = NOAEL/LOAEL/Summed exposure from the applicator and postapplication scenarios separately for dermal and inhalation routes. Dermal MOE was based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and target MOE of 100. Inhalation MOE was based on a LOAEL of 1.9 mg/kg bw/day from an inhalation toxicity study and target MOE of 300. Inhalation exposure was not aggregated with dermal or oral routes as it did not contribute to the common adverse effect.

[d] The highest rate/amount handled was used where MOEs were greater than the target MOE for all routes of exposure for all sub-populations. For broadcast applications, flea and tick scenarios were used, and 'other insects' were used for band/spot treatments.
[e] Postapplication exposure to soft and hard surfaces was greater than that to mattresses, so mattresses were not included.
[f] Inhalation risk assessment was not required for these postapplication scenarios as it qualified for the NAFTA waiver, based on low vapour pressure.
[g] Scenario that resulted in the lowest MOEs
[h] Surface spray aerosol broadcast application by domestic applicators for fleas, ticks, and carpet beetles (0.4% guarantee)
[i] Surface spray aerosol band/spot application by domestic applicators for 'other insects' (1% guarantee)

Table 2 Short-Term Residential Aggregate Exposure and Risk Assessment

Formulation	Postapplication Scenario		Sub-pop	Residential Exposure [a] (mg/kg bw/day)		Dietary Exposure [b] (mg/kg bw/day)	Aggregate MOE [c] (T = 100)
				Dermal	Oral	Oral	Dermal/Oral
Indoor Residential Areas							
Aerosol	0.488 g a.i./m^2 (B)[e] Fleas/ticks	Soft surface	Adults	2.05[d][g]	N/A	0.00750	439
			Youth	1.44[f]		0.00926	582
			Children (1<2)	1.92[f]	0.0180	0.0270	305
		Hard surface	Adults	0.724[d][g]	N/A	0.00750	1050
			Youth	0.383[f]		0.00926	1510
			Children (1<2)	1.28[f]	0.0120	0.0270	406
Aerosol	0.46 g a.i./m^2 (SB)[e] 'Other insects'	Soft surface	Adults	0.969[d]	N/A	0.00750	836
			Youth	0.678		0.00926	1040
			Children (1<2)	0.903	0.00847	0.0270	505
		Hard surface	Adults	0.343[d]	N/A	0.00750	1754
			Youth	0.181		0.00926	2170
			Children (1<2)	0.602	0.00565	0.0270	628

Formulation	Postapplication Scenario		Sub-pop	Residential Exposure [a] (mg/kg bw/day)		Dietary Exposure [b] (mg/kg bw/day)	Aggregate MOE [c] (T = 100)
				Dermal	Oral	Oral	Dermal/Oral
Ready-to-use trigger pump sprayer	0.488 g a.i./m^2 (B) [e] Fleas/ticks	Soft surface	Adults	1.99 [d]	N/A	0.00750	451
			Youth	1.44		0.00926	582
			Children (1<2)	1.92	0.0180	0.0270	305
		Hard surface	Adults	0.665 [d]	N/A	0.00750	1120
			Youth	0.384		0.00926	1510
			Children (1<2)	1.28	0.0120	0.0270	406
Solution	Commercial Applicator (B) 0.091 g a.i./m^2 [e] Fleas/ticks	Soft surface	Adults	0.371	N/A	0.00750	1670
			Youth	0.268		0.00926	1820
			Children (1<2)	0.357	0.00335	0.0270	782
		Hard surface	Adults	0.124	N/A	0.00750	2850
			Youth	0.0715		0.00926	2840
			Children (1<2)	0.238	0.00223	0.0270	889
Lawns and Turf							
Aerosol	Ants		Adults	1.24 [d]	N/A	0.00750	681
			Youth	1.01		0.00926	774
			Children (1<2)	2.00	0.00685	0.0270	330
Ready-to-Use	Perimeter/flea		Adults	0.469 [d]	N/A	0.00750	1436
			Youth	0.377		0.00926	1520
			Children (1<2)	0.747	0.00255	0.0270	608
Gardens and Trees							
Aerosol	Gardens		Adults	0.331 [d]	N/A	0.00750	1792
			Youth	0.138		0.00926	2390
			Children (6<11)	0.164		0.0158	1560
	Trees		Adults	0.114 [d]	N/A	0.00750	2932
			Youth	0.013		0.00926	3410
			Children (6<11)	0.015		0.0158	2030

Formulation	Postapplication Scenario	Sub-pop	Residential Exposure [a] (mg/kg bw/day)		Dietary Exposure [b] (mg/kg bw/day)	Aggregate MOE [c] (T = 100)
			Dermal	Oral	Oral	Dermal/Oral
Pets						
Ready-to-use Shampoo	Small cat[g]	Adults	0.988[d]	N/A	0.00750	823
		Youth	1.18		0.00926	687
		Children (1<2)	2.16	0.00539	0.0270	319

Sub-pop = sub-population; MOE = margin of exposure; T = target MOE; N/A= not applicable; (B) = broadcast application; (SB) = spot/band

[a] Dermal exposure for youth and children from Appendix V, Tables 2, 4-6. Oral exposure for children (1<2 years old) from Appendix V, Tables 16, 18 and 21(hand-to-mouth).

[b] Chronic dietary background exposure.

[c] Aggregate MOE = 1/(1/dermal NOAEL/Residential Exposure)+(1/oral NOAEL/Residential Exposure + dietary exposure)). Dermal MOE was based on a NOAEL of 1000 mg/kg bw/day from a dermal toxicity study and target MOE of 100. Oral MOE was based on a NOAEL of 33 mg/kg bw/day from an oral toxicity study and target MOE of 100. Inhalation exposure was not aggregated with dermal or oral routes as it did not contribute to the common adverse effect.

[d] Exposure from Table 1 above for adults (includes both applicator and postapplication dermal exposure).

[e] The highest rate/amount handled was used where MOEs were greater than the target MOE for all routes of exposure for all sub-populations. For broadcast applications, flea and tick scenarios were used, and 'other insects' were used for band/spot treatments.

[f] Postapplication exposure to soft and hard surfaces was greater than that to mattresses, so mattresses were not included.

[g] Scenario that resulted in the lowest MOEs.

Table 3 Intermediate-Term Residential Aggregate Exposure and Risk Assessment

Formulation	Postapplication Scenario		Sub-pop	Residential Exposure[a] (mg/kg bw/day)		Dietary Exposure [b] (mg/kg bw/day)	ARI[c] (T = 1)
				Dermal	Oral	Oral	Dermal/Oral
Indoor Residential Areas							
Metered release	0.908 g a.i./28 m^3[g]	Soft surface	Adults	0.323	N/A	0.00750	31
			Youth	0.230		0.00926	29
			Children (1<2)	0.311	0.0117	0.0270	8
		Hard surface	Adults	0.108	N/A	0.00750	39
			Youth	0.0623		0.00926	33
			Children (1<2)	0.207	0.00778	0.0270	9

Sub-pop = sub-population; MOE = margin of exposure; T = target ARI; N/A= not applicable

[a] Dermal exposure from Appendix V, Table 8. Oral exposure for children (1<2 years old) from Appendix V, Table 22 (hand-to-mouth).

[b] Chronic dietary background exposure.

[c] ARI = Aggregate Risk Index. ARI = 1/[(Dermal Target MOE/Dermal MOE)+(Oral Target MOE/Oral MOE)]. Dermal MOE = Dermal NOAEL/Dermal exposure. Oral MOE = Oral NOAEL/(residential + dietary exposure). Dermal MOE was based on a NOAEL of 100 mg/kg bw/day from a dermal toxicity study and target MOE of 300. Oral MOE was based on a NOAEL of 33 mg/kg bw/day from an oral toxicity study and target MOE of 100. Inhalation exposure was not aggregated with dermal or oral routes as it did not contribute to the common adverse effect.
[d] Dermal exposure was determined using the application rate. Inhalation exposure was based on the average air concentration (after peak air concentration) from the chemical-specific study (Selim, 2008).

Table 4 Long-Term Residential Aggregate Exposure and Risk Assessment

Formulation	Postapplication Scenario		Sub-pop	Residential Exposure[a] (mg/kg bw/day)		Dietary Exposure [b] mg/kg bw/day)	Aggregate MOE[d] (T = 100)
				Dermal	Oral	Oral	Dermal/Oral
Indoor Residential Areas- Bed bugs							
Aerosol	Commercial Applicator (SB) 0.244 g a.i./m^{2} [d]	Soft surface[e]	Adults	0.00573	N/A	0.00750	559
			Youth	0.00417		0.00926	551
			Children (1<2)	0.00577	0.00187	0.0270	213
		Hard surface[e]	Adults	0.00215	N/A	0.00750	767
			Youth	0.00125		0.00926	704
			Children (1<2)	0.00432	0.00140	0.0270	226

Sub-pop = sub-population; MOE = margin of exposure; T = target MOE; N/A= not applicable; (SB) = spot/band
[a] Dermal exposure from Appendix V. Table 9. Oral exposure from Appendix V. Table 24 (hand-to-mouth).
[b] Chronic dietary background exposure.
[c] Aggregate MOE = 1/(1/dermal NOAEL/Postapplication Exposure)+(1/oral NOAEL/Postapplication Exposure + dietary exposure)). MOE for dermal and oral routes was based on a NOAEL of 7.4 mg/kg bw/day from an oral toxicity study and target MOE of 100 (includes 10% dermal absorption value for the dermal route). Inhalation exposure was not aggregated with dermal or oral routes as it did not contribute to the common adverse effect.
[d] Maximum application rate for bed bugs
[e] Postapplication exposure to soft and hard surfaces was greater than that to mattresses, so mattresses were not included.

Appendix VII Environmental Exposure and Risk Assessment

Table 1 Application Rates of MGK-264 Evaluated in the Risk Assessment

PCP No.	Guarantee (%)	Uses	Sites	Application Rate (g a.i./m^2)	Timing	Application Method
11855	10	Mosquito Abatement	Waste Areas, Roadsides, Residential and Recreational Areas	0.00785	May - September	Truck mounted application equipment
15494	10	Mosquito Abatement	Waste Areas, Roadsides, Residential and Recreational Areas	0.00785	May - September	Truck mounted application equipment
24711	3.33	Mosquito Abatement	Open areas near buildings and in campgrounds	0.00785	May - September	Pressurized spray can to apply in wide sprays across open areas near buildings and campgrounds.
19913	0.4	Outdoor Ornamentals	Ornamental Plants	0.0337	April - early November	Pressurized spray can to outdoor ornamentals.
16063	0.98	Outdoor Domestic Sites	Outdoor	0.0337	May - September	Pressurized spray applied to gardens.
19913	0.4	Outdoor Domestic Sites	Outdoor	0.0337	May - September	Pressurized spray can to shrubs, bushes and grassy areas.
19913	0.4	Outdoor Domestic Sites	Outdoor	0.244	April - early November	Pressurized spray can to wasps and hornet nests.
19913	0.4	Outdoor Domestic Sites	Outdoor	0.244	April - early November	Pressurized spray can to ant hills and trails.
20021	0.167	Outdoor Domestic Sites	Outdoor	0.244	Year round	Spot Treatment: Pressurized spray can to outside surfaces of screens, doors, window frames, foundations, patios, light fixtures and other places where insects may alight, or congregate and enter.
20109	0.25	Outdoor Domestic Sites	Outdoor	0.244	Year round	Spot Treatment: Pressurized spray can to outside surfaces of screens, doors, window frames, foundations, patios, light fixtures and other places where insects may alight, or congregate and enter.
20857	0.25	Outdoor Domestic Sites	Outdoor	0.244	April - early November	Pressurized spray can to ant hills, cracks and crevices in driveways, sidewalks or interlocking brick.
23020	10	Outdoor Domestic Sites	Home - Outdoors	0.091	April - early November	Apply to outside surfaces of buildings, porches, patios, garages and other areas where these pests have been seen or are found.

23020	10	Outdoor Domestic Sites	Home - Outdoors	0.091	April - early November	Building Perimeter Treatment: Treat a 0.5 metre band of soil or other substrate adjacent to buildings (homes) and the building foundation to a height of 0.8 metres where these pests are active and may find entrance.
23020	10	Outdoor Flea Control	Home - Outdoors	0.091	Year round	Areas of lawn where pets normally rest.
27417	0.25	Outdoor Domestic Sites	Ant Hills, Cracks and Crevices in Driveways, Sidewalks or Interlocking Brick Where Ants Hide	0.244	April - early November	Pressurized spray can to ant hills, cracks and crevices in driveways, sidewalks or interlocking brick.
27549	0.167	Outdoor Domestic Sites	Outdoor	0.244	Year round	Spot treatment: Pressurized spray can to outside surfaces of screens, doors, window frames, foundations, patios, light fixtures and other places where insects may alight, or congregate and enter.
28690	0.25	Outdoor Domestic Sites	Opening of Ant Hills, Cracks and Crevices in Driveways, Sidewalks or Interlocking Brick Where Ants Hide	0.244	April - early November	Pressurized spray can to ant hills, cracks and crevices in driveways, sidewalks or interlocking brick.
30837	0.167	Outdoor Domestic Sites	Outdoor	0.244	Year round	Spot treatment: Pressurized spray can to outside surfaces of screens, doors, window frames, foundations, patios, light fixtures and other places where insects may alight, or congregate and enter.

Table 2 Summary Fate and Behaviour of MGK-264 in the Environment

Type of Study	Endpoint	Endpoint Value	Comments
Hydrolysis	Half-life	pH 5: stable pH 7: stable pH 9: stable	Hydrolytically stable. Not an important route of transformation. (PMRA 2673777)
Phototransformation on soil	Half-life	Not reported	Not an important route of transformation. Declined by 18.25% in irradiated samples and 12.26% in dark controls.(net decline = 5.99%) 31 d study @ 25°C with xenon lamp 290-750 nm. (PMRA 2673777)
Phototransformation in water	Half-life	pH 7: stable	Not an important route of transformation. 30 d study @ 25°C with xenon lamp 290-750 nm. (PMRA 2673777)
Transformation in air	Half-life	1.4 hour	No phototransformation data in USEPA RED. Half-life was calculated using EPI Suite software (PMRA 2685603)

Type of Study	Endpoint	Endpoint Value	Comments
Aerobic biotransformation in water/sediment	Not available. Data reserved by USEPA (PMRA 2673777).		
Aerobic biotransformation in soil	Half-life (DT_{50} not reported)	388 d	Persistent (PMRA 2037242). Not an important route of transformation. Half-life (DT_{50} not reported) not reliable because exceeds study duration. 365 d study @ 25°C in dark with sandy loam soil. Eight unidentified transformation products ranging from 1.1 – 15.3% applied radioactivity (AR) were detected. Volatile unidentified residues were 7-12% AR at day 365 and CO_2 was 0.3-0.7% AR. (PMRA 2673777)
Anaerobic biotransformation in soil	DT_{50}	Not reported	Not an important route of transformation. 90 d study @ 25°C in dark with flooded sandy loam soil with nitrogen atmosphere. Declined 14.2% over 60 d (anaerobic period) from 8.05 – 6.91 Φg/g. Four unidentified transformation products occurred in water and soil phases at maximum of 0.4 – 8.6% AR. Volatile unidentified residues were 3.7-5.2% AR @ day 90 and CO_2 was < 0.01% AR. (PMRA 2673777)
Adsorption/Desorption	Koc	686 sand 899 sandy loam 1555 2nd sandy loam 1558 silt loam 3106 clay loam	Low mobility (sand, sandy loam, silt loam) – slight mobility (clay loam). (PMRA 2024011)
Soil leaching	Not available. Data requirement "reserved" by USEPA.		
Volatilization	Not available in USEPA RED.		
Terrestrial Field Dissipation Soil	Not available. Data requirement waived by USEPA.		
Bioconcentration	Not available. Data requirement waived by USEPA.		

Table 3 Physical and Chemical Properties of MGK-264

Properties	Value	Comments
Water solubility	15 mg/L @ 25°C	Soluble in water (PMRA 2673777)
Vapour pressure	2.45×10^{-3} Pa 1.84×10^{-5} mm Hg @ 25°C 9.5×10^{-5} mm Hg @ 25°C (EFED monograph)	Intermediate volatility (PMRA 2673777)
Henry's Law (Constant, K = pressure × molar mass/solubility in water)	K = 4.44 H 10^{-7} atm m^3/mol (based on vapour pressure of 2.45 H 10^{-3}Pa) K = 2.30×10^{-6} atm m^3/mol (based on vapour pressure of 9.5 H 10^{-5} mm Hg @ 25°C EFED monograph) K = 2.85×10^{-7} atm m^3/mol (EFED monograph) Partition coefficient 1/H = 1.07×10^{4} mol (based on vapour pressure of 9.5 H 10^{-5} mm Hg @ 25°C EFED monograph)	Slightly volatile from water or moist soil surfaces. (PMRA 2673777)
pH	6.9 (10 % mixed with water). Typical range 6.8-7.2 6.8-7.2 10% solution	6.9 (10 % mixed with water). Typical range 6.8-7.2 6.8-7.2 10% solution
Dissociation constant (pKa)	Not applicable	Does not contain dissociable moiety (PMRA 1403050)

Properties	Value	Comments
Log octanol/water partition coefficient (Log K_{ow})	3.70 3.61 isomer 1 3.8 isomer 2	Potential to bioaccumulate (PMRA 2673777)
UV/visible absorption spectrum (max)	(λ max = 295 nm)	Not expected to absorb UV at λ_ 300nm (PMRA 1403050)

Table 4 Summary of Abiotic Transformation of MGK-264

Type of study	Half-life	Comments
Hydrolysis	pH 5: stable pH 7: stable pH 9: stable	30 d study 25°C in dark. Not an important route of transformation. Recovery was 97% of AR
Phototransformation (aqueous)	Half-life = stable	Sterile pH 7 aqueous buffer solution irradiated by xenon arc lamp 290-750 nm @ 25°C for 30 days. Stable to phototransformation. Not an important route of transformation USEPA RED. (PMRA 2673777)
Phototransformation (soil)	Half-life = not determined	31 day study of sandy loam at 25°C irradiated with xenon arc lamp (290 – 750 nm). MGK-264 declined from 98.39% to 80.14% (18.25%) AR in irradiated soil and 98.39% to 86.13% (12.26%) in dark controls (Net decline = 5.99%). Not an important route of transformation. No transformation products recovered from irradiated soil or dark controls >1% AR. Half-life not reported in USEPA RED (PMRA 2673777)
Transformation (air)	1.4 hour	Not reported in USEPA RED, calculated using EPI Suite software (PMRA 2685603)

Table 5 Summary of Biotransformation Results for MGK-264

Type of study	Transformation Rate	Comments
Aerobic biotransformation (soil)	Half-life 388 d (DT_{50} not reported) (value not reliable) DT_{90} not reported	Persistent. Not an important route of transformation. DT_{50} not reported. Since half-life exceeds duration of study half-life value is not reliable. 365 d study 25°C in dark with sandy loam soil @ 70-75% field moisture capacity. Treated @ 8.7-9.6 µg/g MGK-264. Eight unidentified transformation products ranging from 1.1 – 15.3% AR were detected. Volatile unidentified residues were 7-12% AR at day 365 and CO_2 was 0.3-0.7% AR. (PMRA 2673777)
Anaerobic biotransformation (soil) (water/soil system)	DT_{50} > not reported	Not an important route of transformation. 90 d study @ 25°C in dark with flooded sandy loam soil with nitrogen atmosphere. Declined 14.2% over 60 d (anaerobic period) from 8.05 – 6.91 Φg/g. Four unidentified transformation products occurred in water and soil phases at maximum of 0.4 – 8.6% AR. Volatile unidentified residues were 3.7-5.2% AR @ day 90 and CO_2 was < 0.01% AR. (PMRA 2673777)
Aerobic aquatic biotransformation (water/sediment)	Not data available.	Data requirement reserved by USEPA (PMRA 2673777)
Anaerobic aquatic biotransformation (water/sediment)	Not data available.	Data requirement reserved by USEPA (PMRA 2673777)

Table 6 Summary of Acute and Chronic Toxicity Endpoints Reported for Non-Target Organisms

Species	Exposure (%)	Endpoint Observed	Value	Comments
Acute Terrestrial				
Honey bee (*Apis mellifera*)	No data (USEPA requested data on acute contact toxicity study due to lawn/turf/ornamental plants exposure but not submitted, PMRA 2673777)			
Earthworm (*Eisenia foetida*)	No data available			
Beneficial arthropods	No data available			
Northern bobwhite quail (*Colinus virginianus*)	Technical MGK (93.1)	14-d LD_{50}	**> 2250 mg a.i./kg bw**	No mortality at any treatment level (PMRA 2673777)
Mallard duck (*Anas platyrhynchos*)	Technical MGK (92.9)	14-d LD_{50}	> 2250 mg a.i./kg bw	No mortality at any treatment level (PMRA 2673777)
Northern bobwhite quail (*Colinus virginianus*)	Technical MGK (92.9)	5-d LC_{50}	**>5620 mg a.i./kg diet**	No mortality at any treatment level (PMRA 2673777)
Mallard duck (*Anas platyrhynchos*)	Technical MGK (92.9)	5-d LC_{50}	>5620 mg a.i./kg diet	No mortality at any treatment level (PMRA 2673777)
Rat (*Rattus norvegicus*)	Formulated product (% a.i. not specified)	LD_{50}	>20,000 mg a.i./kg bw	(PMRA 2673777)
Rat (*Rattus norvegicus*) (Subacute dietary)	No data available			
Toxicity to Vascular plants	Not required			
Reproductive				
Northern bobwhite quail (*Colinus virginianus*)	No data (USEPA requested data but not submitted, PMRA 2673777)			
Mallard duck (*Anas platyrhynchos*)	No data (USEPA requested data but not submitted, PMRA 2673777)			
Rat (*Rattus norvegicus*)	Not specified	NOEL	**<62.5 mg a.i./kg bw**	Mulitgenerational study. Endpoint pup wt gain.
Acute Aquatic				
Daphnia magna	Technical MGK (92.1%)	48-h LC_{50}	2.3 mg a.i./L	(PMRA 2673777)
Rainbow trout (*Oncorhynchus mykiss*)	Technical MGK (92.1%)	96-h LC_{50}	1.4 mg a.i./L	(PMRA 2673777)
Bluegill sunfish (*Lepomis macrochirus*)	Technical MGK (92.1%)	96-h LC_{50}	2.4 mg a.i./L	(PMRA 2673777)
Amphibians	No data available, rainbow trout endpoint used as surrogate			
Freshwater Algae (Acute)	No data available			
Freshwater Plants (Acute)	No data available			
Estuarine/Marine Invertebrates (Acute)	No data available (USEPA requested data but not submitted, PMRA 2673777)			
Estuarine/Marine Fish (Acute)	No data available (USEPA requested data but not submitted, PMRA 2673777)			
Estuarine/Marine Algae (Acute)	No data available			
Chronic Aquatic				
Freshwater Invertebrates (Chronic)	No data available			
Estuarine/Marine Invertebrates (Chronic)	No data available			
Estuarine/Marine Fish (Chronic)	No data available			

Table 7 Avian Acute Oral Toxicity of MGK-264

Species Tested	% a.i.	LD_{50} (mg a.i./kg bw)	Comments
Bobwhite quail (*Colinus virginianus*)	93.1	>2250	Practically non-toxic
Mallard duck (*Anas platyrhynchos*)	92.9	>2250	Practically non-toxic

Table 8 Avian Subacute Dietary Toxicity of MGK-264

Species Tested	% a.i.	5- d LC_{50} (mg a.i./kg diet)	Comments
Bobwhite quail (*Colinus virginianus*)	92.9	> 5620	Practically non-toxic
Mallard duck (*Anas platyrhynchos*)	92.9	>5620	Practically non-toxic

Table 9 Mammalian Acute Oral Toxicity of MGK-264

Species Tested	% a.i.	LD_{50} (mg a.i./kg bw)	Comments
Rat (*Rattus norvegicus*)	Formulated product	> 20,000	Practically non-toxic

Table 10 Mammalian Reproductive Toxicity of MGK-264

Species Tested	% a.i.	Endpoint	Comments
Rat (*Rattus norvegicus*)	Not specified	NOEL < 60.9 mg a.i./kg bw	Multi-generation repro study. Endpoint pup wt gain.

Table 11 Freshwater Invertebrate Acute Toxicity of MGK-264

Species Tested	% a.i.	48-h LC_{50} (mg a.i./L)	Comments
Water flea (*Daphnia magna*)	92.9	2.3	Moderately toxic (PMRA 2673777)

Table 12 Freshwater Fish Acute Toxicity of MGK-264

Species Tested	% a.i.	96-h LC_{50} (mg a.i./L)	Comments
Rainbow trout (*Oncorhynchus mykiss*)	92.1	1.4	Moderately toxic (PMRA 2673777)
Bluegill sunfish (*Lepomis macrochirus*)	92.1	2.4	Moderately toxic (PMRA 2673777)

Table 13 Endpoints Used for Risk Assessment and the Species Uncertainty Factors Applied

Taxonomic group	Exposure	Endpoint	Endpoint Value from Toxicity Data	Species Uncertainty Factor Applied	Endpoint Used in Risk Assessment
Earthworm	Acute	LC_{50}	No data		
	Chronic	NOEC			
Bees	Acute	LD_{50}	No data		
Other Non-Target Arthropods	Acute	LR_{50}	No data		
Birds	Acute oral	5-d LC_{50}	>2250 mg a.i./kg diet	1/10	562 mg a.i./kg bw
	Dietary	14-d LD_{50}	> 5620 mg a.i./kg bw	1/10	225 mg a.i./kg diet
	Reproduction	NOEL	No data		
Mammals	Acute oral	LD_{50}	>20,000 mg a.i./kg bw	1/10	2000 mg a.i./kg bw/day
	Reproduction	NOEL	<62.5 mg a.i./kg bw	1	62.5 mg a.i./kg bw/day
Non-Target Terrestrial Plants	Acute	EC_{25}	No data		
Aquatic Invertebrates	Acute - freshwater	48-h LC_{50}	2.3 mg a.i./L	1/2	1.15 mg a.i./L
	Acute - sediment	LC_{50} or EC_{50}	Not available		
	Chronic - freshwater	NOEC			
	Acute - marine	LC_{50} or EC_{50}			
Fish	Acute - freshwater	96-h LC_{50}	1.4 mg a.i./L	1/10	0.14 mg a.i./L
	Chronic - freshwater	No data			
	Acute - marine				
Amphibians	Acute	Fish LC_{50}	1.4 mg a.i./L	1/10	0.14 mg a.i./L
	Chronic	Fish NOEC	No data		
Algae	Acute - freshwater	EC_{50}	No data		
	Acute - marine	EC_{50}			
Aquatic Vascular Plants	Chronic	EC_{50}	No data		

Table 14 Screening Level Risk of MGK-264 to Birds

	Toxicity (mg a.i./kg bw/d)[a]	Feeding Guild (Food Item)	EDE (mg a.i./kg bw)[b]	RQ	LOC Exceeded ?
Small Bird (0.02 kg)					
Acute	225.00	Insectivore	16.62	0.07	N
Medium Sized Bird (0.1 kg)					
Acute	225.00	Insectivore	12.97	0.06	N
Large Sized Bird (1 kg)					
Acute	225.00	Herbivore (short grass)	8.38	0.04	N

[a] Toxicity values for the acute exposure have been adjusted with an uncertainty factor of 0.1.
[b] EDE = Estimated dietary exposure; is calculated using the following formula: (FIR/BW) × EEC, where:
FIR: Food Ingestion Rate (Nagy, 1987). For generic birds with body weight less than or equal to 200 g, the

"passerine" equation was used; for generic birds with body weight greater than 200 g, the "all birds" equation was used:
Passerine Equation (body weight < or =200 g): FIR (g dry weight/day) = 0.398(BW in g)$^{0.850}$
All birds Equation (body weight > 200 g): FIR (g dry weight/day) = 0.648(BW in g)$^{0.651}$.
For mammals, the "all mammals" equation was used: FIR (g dry weight/day) = 0.235(BW in g)$^{0.822}$
BW: Generic Body Weight
EEC: Concentration of pesticide on food item based on Hoerger and Kenaga (1972) and Kenaga (1973) and modified according to Fletcher et al. (1994). At the screening level, relevant food items representing the most conservative EEC for each feeding guild are used.

Table 15 Screening Level Risk of MGK-264 to Mammals

	Toxicity (mg a.i./kg bw/d)	Feeding Guild (Food Item)	EDE (mg a.i./kg bw)	RQ	LOC Exceeded?
Small Mammal (0.015 kg)					
Acute	2000.00	Insectivore	9.56	0.00	No
Reproduction	62.50	Insectivore	9.56	0.15	No
Medium Sized Mammal (0.035 kg)					
Acute	2000.00	Herbivore (short grass)	18.54	0.01	No
Reproduction	62.50	Herbivore (short grass)	18.54	0.30	No
Large Sized Mammal (1 kg)					
Acute	2000.00	Herbivore (short grass)	9.91	0.00	No
Reproduction	62.50	Herbivore (short grass)	9.91	0.16	No

Table 16 Screening Level Surface Water EECs

Application Rate g a.i./ha (mosquito abatement)	Number of Applications per Season	Interval between Applications (days)	EEC 80 cm depth (mg a.i./L)	EEC 15 cm depth (mg a.i./L)
78.5	20	7	0.172	0.93

Table 17 Screening Level Risk of MGK-264 to Aquatic Organisms

Taxonomic group	Exposure	Endpoint	Surface Water		LOC Exceeded?
			EEC (mg a.i./L)	RQ (EEC/endpoint)	
Aquatic invertebrates	Acute – freshwater	48-h LC_{50} 1.15 mg a.i./L	0.17	0.15	**No**
Fish	Acute – freshwater	96-h LC_{50} 0.14 mg a.i./L	0.17	**1.2**	**Yes**
Amphibians	Acute fish	LC_{50} 0.14 mg a.i./L	0.93	**6.6**	**Yes**

Table 18 Tier 1 Level Risk of MGK-264 to Aquatic Organisms from Mosquito Abatement Uses

Direct overspray from surface water using 90th centile of daily average concentrations

Organism	Exposure	Endpoint	Direct Overspray from Mosquito Abatement Uses*		LOC exceeded?
			EEC (mg a.i./L)	RQ (EEC/endpoint)	
Daphnia magna	Acute 48-h LC_{50}	48-h LC_{50} – 1.15 mg a.i./L	0.026	0.23	No
Rainbow trout	Acute 96 hr	96-h LC_{50} – 0.14 mg a.i./L	0.026	0.19	No
Amphibians	Acute 96 hr (from rainbow trout acute)	LC_{50} – 0.14 mg a.i./L	0.026	0.19	No

*general outdoor and mosquito abatement (20 × 78.5 g a.i./ha at 7-day intervals)

Table 19 Toxic Substances Management Policy Considerations - Comparison to TSMP Track 1 Criteria

TSMP Track 1 Criteria	TSMP Track 1 Criterion Value		Active Ingredient Endpoints*	Transformation Products Endpoints
CEPA toxic or CEPA toxic equivalent	Yes		-	-
Predominantly anthropogenic	Yes		-	-
Persistence	Soil	Half-life ≥ 182 days	Half-life 388 d	Not available
	Water	Half-life ≥ 182 days	Half-life not reported	Not available
	Sediment	Half-life ≥ 365 days	Half-life not reported	Not available
	Air	Half-life ≥ 2 days or evidence of long range transport	Volatilization is the main route of dissipation based on the MGK-264 vapour pressure (2.4 % 10-3 Pa at 25°C) and Henry's Law Constant (4.44 % 10-7 atm m3/mol).	Not available
Bioaccumulation	Log $K_{OW} \geq 5$		Log K_{OW} 3.70	Data were not available and will not be required as MGK-264 is applied as an ULV spray mist. PMRA does not expect that MGK-264 to persist in air or deposit to terrestrial or aquatic habitat, therefore, MGK-264 is not expected to be available for bioaccumulation.
	BCF ≥ 5000		No data available	Not available
	BAF ≥ 5000		No data available	Not available
Is the chemical a TSMP Track 1 substance (all four criteria must be met)?			No	No

Appendix VIII Label Amendments for End-Use Products Containing MGK-264

The label amendments presented below do not include all label requirements for individual end-use products, such as first aid statements, disposal statements, precautionary statements and supplementary protective equipment. Information on labels of currently registered products should not be removed unless it contradicts the following label statements. **Note:** The following information is divided according to product type. Please read each section carefully and make appropriate changes to your product labels.

I) TECHNICAL GRADE ACTIVE INGREDIENTS

No additional mitigation measures are proposed.

II) DOMESTIC-CLASS PRODUCTS

The following domestic-class products are proposed for cancellation:

- Dust products
- Metered release aerosol products

The following domestic-class uses are proposed for cancellation:

- Space spray uses from aerosol products

For all domestic-class products, the following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are already present:

> "DO NOT apply to overhead areas or while in confined spaces (attics, crawlspaces, etc.)."
>
> "DO NOT allow people or pets to re-enter treated areas until sprays have dried." OR "Avoid contact with treated animals until dried." (for products directly applied to pets)

For all domestic-class products, the following statement is proposed to be added under **DIRECTIONS FOR USE**:

> "Cover or remove exposed food and food handling surfaces prior to application".

For aerosol products registered for indoor treatment of fleas, ticks, and carpet beetles, such as Raid Flying Insect Killer Pressurized Spray (PCP No. 15411), the maximum guarantee is proposed to be limited to 0.4% MGK-264.

For indoor structural pest control products, such as Lloyds Crawling Insect Killer Pressurized Contact and Residual Spray (PCP No. 24766):

The following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are already present:

"Ventilate treated areas either by opening windows and doors or through use of air exchange/ventilation systems. Use fans where required to aid in the circulation of air."

Statements regarding application methods, such as those below, may be added to product labels, unless similar information or more restrictive application instructions are already present:

"Broadcast applications are defined as application of a pesticide to broad expanses of surfaces such as walls, floors, ceilings and foundation walls. Broadcast applications should be evenly distributed and not applied beyond the point of run-off."

"Band treatment is defined as a spray of pesticide into the cracks and crevices where pests hide or through which they may enter a building. This includes around the outside edges of a room (baseboards), doorways and/or windows."

"Spot treatment is defined as a low pressure spray of pesticide to a localized or specific surface area not greater than 0.2 m^2 (2 ft^2). Spots are not to be adjoining (contiguous) and the total area of spots is not to exceed 10% of the surface area being treated (e.g. carpets, exterior walls)."

III) COMMERCIAL-CLASS PRODUCTS

For all commercial-class products, the following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are already present:

"DO NOT apply by handheld mistblower or fogger."

"DO NOT apply to overhead areas or in confined spaces without goggles and a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides, unless more restrictive personal protective equipment is required when using the product."

"DO NOT allow people or pets to enter treated areas until sprays have dried." OR "Avoid contact with treated animals until dried." (for products directly applied to pets) These statements do not apply to products applied as an indoor space spray where a more restrictive statement is specified below.

For all commercial-class products, the following statements are proposed to be added under **DIRECTIONS FOR USE**:

"Cover or remove exposed food and food handling surfaces prior to application."

"Application on livestock intended for food production is prohibited."

For structural pest control products applied as an indoor surface spray, such as K-G Insecticide I (PCP No. 24400):

The following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are already present:

> "Wear long-sleeved shirt, long pants, shoes and socks during mixing, loading, application, clean-up and repair."
>
> "For application using handheld equipment, applicators must also wear chemical-resistant gloves."
>
> "During indoor application, applicators must also wear a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."
>
> "Ventilate treated areas either by opening windows and doors or through use of air exchange/ventilation systems confirmed to be operational. Use fans where required to aid in the circulation of air."

Statements regarding application methods, such as those below, may be added to product labels, unless similar information or more restrictive application instructions are already present:

> "Broadcast applications are defined as application of a pesticide to broad expanses of surfaces such as walls, floors, ceilings and foundation walls/crawlspaces. Broadcast applications should be evenly distributed and not applied beyond the point of run-off."
>
> "Band treatment is defined as a low pressure spray of pesticide (do not exceed 345 kPa (50 psi)) in a band or strip (less than 0.3 m wide) around the outside edges of a room (baseboards, ceiling), doorways and/or windows."
>
> "Spot treatment is defined as a low pressure spray of pesticide (do not exceed 345 kPa (50 psi)) to a localized or specific surface area not greater than 0.2 m^2 (2 ft^2). Spots are not to be adjoining (contiguous) and the total area of spots is not to exceed 10% of the surface area being treated (e.g. carpets, exterior walls)."

For products applied as an indoor space spray, and that are not metered release aerosol products, such as Pyrocide 300 (PCP No. 13779):

The following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are not already present:

> "Wear long-sleeved shirt, long pants, shoes and socks during mixing, loading, application, clean-up and repair."
>
> "For application using handheld equipment, applicators must also wear chemical-resistant gloves."

"During indoor application, applicators must also wear a respirator with a NIOSH approved organic-vapour-removing cartridge with a prefilter approved for pesticides OR a NIOSH approved canister approved for pesticides."

"DO NOT apply by handheld ULV aerosol generators or mechanical aerosol generators."

"Do not allow people to enter treated areas until 2 hours after application. The commercial applicator is responsible for informing the homeowner, workers, etc of this requirement."

"Ventilate 2 hours after treatment either by opening windows and doors or through use of air exchange/ventilation systems confirmed to be operational. Use fans where required to aid in the circulation of air."

The following statement is proposed to be added on the **PRIMARY LABEL** and under **PRECAUTIONS** when the application rate for indoor space spray is greater than 0.055 g a.i./m^3:

"DO NOT apply as an indoor space spray at rates greater than 0.055 g a.i./m^3 in dwellings, such as houses, apartments, or in guest rooms of hotels, motels, and resorts."

For metered release aerosol products applied as an indoor space spray, such as Konk 409 Flying Insect Killer (PCP No. 20463):

The maximum guarantee is proposed to be limited to 3.3% MGK-264.

The following statement is proposed to be added on the **PRIMARY PANEL** and under **PRECAUTIONS**:

"DO NOT use in dwellings (e.g. houses, apartments) or in rooms attached to dwellings (e.g. garage, basement), schools, daycare centers, children's hospital wards, guest rooms of hotels, motels, and resorts, or any area where children may spend more than 4 hours in a day."

For outdoor structural pest control products, such as Evercide Intermediate 2507 (PCP No. 23020):

The following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are already present:

"Wear long-sleeved shirt, long pants, shoes and socks during mixing, loading, application, clean-up and repair."

"For application using handheld equipment, applicators must also wear chemical-resistant gloves."

For outdoor mosquito control products, such as Gardex Industrial Microspray Concentrate (PCP No. 11855):

The following statements are proposed to be added under **PRECAUTIONS**, unless similar or more protective statements are already present:

"Wear long-sleeved shirt, long pants, shoes and socks during mixing, loading, application, clean-up and repair."

"For application using handheld equipment, applicators must also wear chemical-resistant gloves."

"For application using truck-mounted equipment, applicators must use an enclosed truck cab with rolled up windows or wear a chemical-resistant hat that covers the neck (e.g. Sou'Wester). For enclosed cabs, chemical-resistant gloves are not required to be worn inside the cab during application but are required for clean-up, calibration and repair. If the cab is not enclosed, then chemical-resistant gloves also need to be worn during application."

"Apply only when the potential for drift to non-target areas of human habitation or non-target areas of human activity such as houses, cottages, schools, and recreational areas is minimal. Take into consideration wind speed, wind direction, temperature inversions, application equipment, and sprayer settings."

References

A. Information Considered in the Chemistry Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1418863	1988. Physical and Chemical Properties Test Requirements for Product Chemistry of MGK-264, Insecticide Synergist, DACO: 2.14
1418765	1988. Determination of Ambient Vapor Pressure of MGK-264, DACO: 2.14.
1238020	Estimation of Octanol/Water Partition Coefficient of MGK-264 (35545), DACO: 8.2.1.
1418767	1986. Description of Beginning Materials and Manufacturing Process, DACO: 2.13.
2450362	2014. Certificate of Analysis/PQR, DACO: 2.11.2.
2450363	2014. Certificate of Analysis, DACO: 2.11.2.
2450364	2013. Certificate of Analysis, DACO: 2.11.2.
2450365	2014. Summary of Manufacturing Process for MGK-264 Insecticide Synergist, DACO: 2.11.3.
1418763	1992. Product Chemistry, DACO: 2.11.
2358205	2010. Preliminary Analysis of Technical MGK-264 Insecticide Synergist, DACO: 2.13.3.
1418764	1992. Formal Report of Analysis in MGK-264, Technical, DACO: 2.13.4.

B. Information Considered in the Toxicological Assessment

List of Studies/Information Submitted by Registrant

PMRA Document Number	Reference
1157148	1982. Summary of results of Acute Toxicity Studies (81-2837a)(Primary Skin Irritation & Guinea Pig Sensitization) (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.2.5,4.2.6.
1157149	Goldenthal, E. 1993. 24-Month Dietary Chronic Toxicity and Oncogenicity study in the Rat with MGK-264 (551-030) (*N*-Octyl Bicycloheptene Dicarboximide), Published by International Research and Development Corporation., DACO: 4.4.2.
1157152	Goldenthal, E. 1993. 24-Month Dietary Chronic Toxicity and Oncogenicity study in the rat with MGK-264 (551-030) (*N*-Octyl Bicycloheptene Dicarboximide), Published by International Research and Development Corporation., DACO: 4.4.1.

1157153	1987. Chromosome Aberrations In Chinese Hamster Ovary (CHO) Cells with a Confirmatory Assay - Final Report (T5205.337001) (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.5.4.
1157154	L5178y Tk+/- Mouse Lymphoma Mutagenesis Assay - Final Report (T5205.701020) (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.5.4.
1157155	1990. Unscheduled DNA Synthesis in Rat Primary Hepatocytes (Part of Final Report to be Amended)(T5205.380026)(*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.5.4.
1157156	1986. Salmonella/Mammalian Microsome Plate Incorporation Mutagenicity Assay (Ames Test) with a Confirmatory Assay (T52058.501014) (*N*-Octyl Bicycloheptene Dicarboximide), Study Director: Timothy E. Lawlor; Lab Supervisor: Valentine O. Wagner; Biologist: Bradley E. Carter, et al., Published by Microbiological Associates Inc., DACO: 4.5.4.
1157157	1994. Summary of Completed Toxicology Studies Conducted with MGK-264 (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.1.
1157158	1991. Summary of Results of Acute Toxicity Studies (91-7238a) (*N*-Octyl Bicycloheptene Dicarboximide) (Acute Dermal LD50 Male/Female Rabbits; Eye Irritation In 6/6 Albino Rabbit), DACO: 4.2.4.
1157160	1987. Summary of Results of Acute Oral Toxicity Study (in Male/Female Albino Rats)(87-5655a) (*N*-Octyl Bicyloheptene Dicarboximide), DACO: 4.2.1.
1157161	1985. Summary of Results of an Acute Inhalation Toxicity LC_{50} Study in Male/Female Albino Rats (84-4334a) (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.2.3.
1157162	Newton, E. 1994. A Subchronic (3-Month) Inhalation Toxicity Study Of MGK-264 Insecticide Synergist in the Rat via Whole-Body Exposures Final Report (91-8364) (*N*-Octyl Bicycloheptene Dicarboximide), Submitted to McLaughlin Gormley King Company, DACO: 4.3.6.
1157163	1992. One Year Dietary Toxicity Study in Dogs with MGK-264 (551-031) (*N*-Octyl Bicycloheptene Dicarboximide), Published by International Research Development Corporation, DACO: 4.4.1.
1157164	1990. Developmental Toxicity Study in Rats (551-026) (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.5.2.
1157166	Blair, M. 1987. 13-Week Dietary Range-Finding Toxicity Study In Mice With MGK-264 Insecticide Synergist (Amended Report) (551-010) (*N*-Octyl Bicycloheptene Dicarboximide) (N.B. 10 pages are missing- Various page numbers), Study Amended: October 24, 1991., DACO: 4.3.1.
1157167	1987. Teratological Study of MGK-264 Insecticide Synergist Administered Orally to Albino Rabbits (551-015) (*N*-Octyl Bicycloheptene Dicarboximide), DACO: 4.5.2.
1157168	Schardein, J.L. 1989. Range-Finding Developmental Toxicity Study in Rats (551-025) (*N*-Octyl Bicycloheptene Dicarboximide), Published by International Research and Development Corporation, DACO: 4.5.2.
1157169	1986. Range-Finding Teratology Study in Rabbits with MGK-264 Insecticide Synergist (551-014) (*N*-Ocytl Bicycloheptene Dicarboximide), DACO: 4.5.2.

1157170	Blair, M. 1991. Eighteen Month Dietary Oncogenicity Study in Mice with MGK-264 Insecticide Synergist (551-011) (*N*-Octyl Bicycloheptene Dicarboximide), Published by International Research and Development Corporation, DACO: 4.4.1, 4.4.2.
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